ROLE OF DEPRESSIVE SYMPTOMS IN CARDIOVASCULAR DISEASE, COGNITIVE DECLINE, AND MORTALITY

by
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ABSTRACT

Background and Purpose: Depression is increasingly prevalent as adults age, but is undertreated in older adults. As populations in the US and the world are aging, it is important to evaluate the contributions of depression to cardiovascular risk factors, cognitive decline, and mortality. The proposed study will examine avenues by which vascular depression is associated with cognitive decline, dementia, and all-cause mortality. First, we will examine the timing of the effect of vascular burden and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, ever smoking status, and overweight/obesity status) on onset of late-life depression. We will then determine whether depressive symptoms partially mediate the association of subclinical cardiovascular disease (CVD) with cognitive decline and dementia. Finally, we will evaluate the indirect effect of persistent depressive symptoms on the association between subclinical CVD and all-cause mortality.

Methods: We investigated the effect of vascular burden and cardiovascular risk factors on the onset of late-life depression, using 1,190 former male medical students from the Johns Hopkins Precursors Study. Cox proportional hazards models using discrete time were used to evaluate the effect of vascular burden and cardiovascular risk factors occurring before and after age 65 on the onset of depression. Competing risks analysis, using the Long and Gray method, were used to account for the competing risk of mortality in later life. Also, we examined the role of persistent depressive symptoms as potential mediators in the associations of subclinical cardiovascular disease with onset of mild cognitive impairment (MCI) and dementia as well as all-cause mortality. To this, we

applied the counterfactual approach to causal mediation using time-to-event data from the Cardiovascular Health Study. Accelerated failure time models with Weibull distribution were used to examine the total, direct, and indirect effects of the association between subclinical CVD and MCI/dementia onset via persistent depressive symptoms, since the proportionality hazard assumption was not met. Cox proportional hazards models were used to evaluate total, direct, and indirect effects of subclinical cardiovascular disease on all-cause mortality via persistent depressive symptoms, since the proportionality hazard assumption was met. Both models were weighted by estimates of multivariable logistic regression models of persistent depressive symptoms on subclinical cardiovascular disease and baseline covariates.

Results: Diabetes, hypertension, and hyperlipidemia before age 65 as well as vascular burden and diabetes after age 65 were associated with incident depression after age 65 among participants who were depression-free up to age 65. Cardiovascular risk factors and vascular burden before age 65 were not associated with incident depression up at age 65 with the exception of overweight/obese status having a protective effect against incident depression. Persistent depressive symptoms partially mediated the association between subclinical CVD with MCI/dementia onset, not all-cause mortality. Subclinical CVD was an independent risk factor of all-cause mortality.

Conclusions: These results support the vascular depression hypothesis. Findings suggest that screening and treatment of depressive symptoms may reduce or delay the risk of incident MCI and dementia in older adults with subclinical CVD. Moreover, subclinical

CVD was a strong predictor of all-cause mortality, independent of persistent depressive symptoms. Subclinical CVD and persistent depressive symptoms may lead to all-cause mortality on different pathways. Future directions involve the evaluation of domains of depressive symptoms and their potential mediating roles in common disease pathways in older adults.

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Abbreviations

3MS – Modified Mini-Mental State Examination
AD – Alzheimer's disease
BMI – Body Mass Index
CHS – Cardiovascular Health Study
CES-D – The Center for Epidemiologic Studies - Depression Scale
COAH – Center on Aging and Health
CVD – Cardiovascular disease
ICD-9 – *International Classification of Diseases, Ninth Revision*
MCI – Mild Cognitive Impairment
MMSE – Mini Mental Status Examination
MRI – Magnetic Resonance Imaging
PHQ-9 – Patient Health Questionnaire-9
TICS – Telephone Interview for Cognitive Status

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SPECIFIC AIMS

The mechanisms underlying the relationship among cardiovascular disease (CVD), depression, dementia, and all-cause mortality are not well-understood (Almeida, Alfonso, Flicker, Hankey, & Norman, 2012; Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Barnes et al., 2012; Becker et al., 2009; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Sheline et al., 2006). Mood disorders have been hypothesized as potential underlying mechanisms of associations of CVD with dementia and all-cause mortality, since depressive symptoms can often co-occur with CVD, and both are prevalent in older adults (Alexopoulos, 2010; Alexopoulos et al., 1997; Steffens, Helms, Krishnan, & Burke, 1999; Steffens, Krishnan, Crump, & Burke, 2002; Taylor, Aizenstein, & Alexopoulos, 2013). This notion is embodied in the vascular depression hypothesis: CVD leads to, maintains, or exacerbates depression in older adults (Alexopoulos et al., 1997). Common causes of depression and CVD are cardiovascular risk factors, which include diabetes, hypertension, hyperlipidemia, ever smoking status, and overweight/obese status.

Depression, CVD, and cardiovascular risk factors are associated with greater risk and severity of cognitive decline and dementia (Barnes et al., 2006; Luchsinger et al., 2005). People with three or more cardiovascular risk factors are more likely to have Alzheimer's disease (AD) than those with less than three cardiovascular risk factors (Luchsinger et al., 2005). Depressive symptoms in later life (65 years and older) are associated with a two-fold increase in risk of developing AD and a three-fold increase in risk of developing dementia related to vascular disease (Luchsinger et al., 2005). Besides

its relationship with cognitive decline and dementia, depression is an independent risk factor for mortality in older adults (Schulz et al., 2000).

Although studies have examined late-onset depression as underlying mechanisms of the association between CVD and dementia in older adults (Barnes et al., 2006; Sheline et al., 2006), we will examine whether modifiable cardiovascular risk factors throughout the life course could lead to depressive symptoms in older adults. Moreover, this study will elucidate vascular mechanisms leading to changes in cognitive function and mortality by evaluating the mediating role of depressive symptoms in CVD, cognition, and all-cause mortality.

This study will use data from the Johns Hopkins Precursors Study, a prospective cohort of 1,337 former medical students for Specific Aim 1. For Specific Aims 2 and 3, data from the Cardiovascular Health Study (CHS), a geographically diverse prospective cohort study of 5,888 community-dwelling older men and women, will be used.

Specific Aim 1: To compare the temporal associations between cardiovascular risk factors and incident depression before and after age 65.

Hypothesis: There is a positive association of cardiovascular risk factors and vascular burden occurring before age 65 and onset of depression after age 65, not before age 65.

Specific Aim 2: To determine whether persistent depressive symptoms partially mediate the association of subclinical cardiovascular disease with onset of mild cognitive impairment and dementia.

Hypothesis: Persistent depressive symptoms partially mediate the association of subclinical cardiovascular disease with the onset of mild cognitive impairment and dementia.

Specific Aim 3: To evaluate whether persistent depressive symptoms partially mediate the association between subclinical cardiovascular disease and all-cause mortality.
Hypothesis: Persistent depressive symptoms partially mediate the association between subclinical cardiovascular disease and all-cause mortality.

OVERVIEW

The following background section begins with an introduction to the epidemiology of depression in older adults and barriers to care for depression. Next, the vascular depression hypothesis is defined and discussed. The vascular depression hypothesis postulates that CVD leads to, maintains, or exacerbates depression in older adults. With these notions, we linked CVD and depression to two outcomes: onset of mild cognitive impairment and dementia as well as all-cause mortality. This section concludes with how cardiovascular disease and depression are associated with onset of mild cognitive impairment and dementia as well as all-cause mortality.

The topic of the first manuscript is to compare temporal associations of cardiovascular risk factors and incident depression before and after age 65. It is unclear if cardiovascular risk factors and vascular burden before age 65 lead to onset of incident depression before age 65. It is also unclear the degree to which cardiovascular risk factors and vascular burden before age 65 lead to an increased risk of the development of newly incident depression after age 65.

In the second manuscript, persistent depressive symptoms may partially mediate the association of subclinical CVD with onset of mild cognitive impairment and dementia. If there is an indirect effect of persistent depressive symptoms on the association of subclinical CVD with onset of mild cognitive impairment and dementia, then those at risk for developing clinical cardiovascular disease may delay onset of mild cognitive impairment and dementia by treatment and intervention on depressive symptoms. If there is no indirect effect, then subclinical cardiovascular disease and

persistent depressive symptoms may independently lead to onset of mild cognitive impairment and dementia.

In the third manuscript, we evaluated the indirect effect of persistent depressive symptoms on the association between subclinical CVD and all-cause mortality. If there is an indirect effect of persistent depressive symptoms on the association between subclinical CVD and all-cause mortality, then those with subclinical cardiovascular may decrease risk of death by intervening on depressive symptoms. If there is no indirect effect, then it is conceivable that both subclinical CVD and persistent depressive symptoms lead to risk of all-cause mortality independently.

INTRODUCTION

Epidemiology of late-life depression

By 2050, there will be an estimated 83.7 million adults aged 65 and older in the United States, representing over 20 percent of the population (Ortman, Velkoff, & Hogan, 2014). Depressive symptoms are more common with advanced age, and the prevalence of depression doubles after age 80 (García-Peña et al., 2013). Among community-dwelling older adults, the prevalence of depressive symptoms in the past year is approximately 15% (Mulsant & Ganguli, 1999). The prevalence of both depressive symptoms and major depressive episodes rise to 20% and 12% respectively in primary care, 25% and 15% in acute care settings, and 40% and 16% in nursing home care settings (Mulsant & Ganguli, 1999). Depression is one of the leading causes of disability, and older adults are at elevated risk of both depression and dementia (Gonzalez, Tarraf, Whitfield, & Gallo, 2012).

Presentation of depression differs between those aged 65 and older (later life) and those younger than 65. Those with depression in later life are more likely to have comorbidities, develop apathy, and show greater white matter hyperintensities as noted in MRIs, while those with depression before 65 years of age are more likely to have an increased genetic risk, psychiatric comorbidity, and cognitive vulnerability (Baldwin & O'Brien, 2002; McDermott & Ebmeier, 2009; Potter & Steffens, 2007; Schulz et al., 2000; Steffens et al., 1999). Those with early-onset depression have shown impairment in episodic memory, whereas those with late-life depression have developed deficits in both executive function and processing speed (Alexopoulos et al., 2001; Ganguli, 2009; Jorm, 2010; McDermott & Ebmeier, 2009).

Barriers to care for depression

Depression is under-recognized and undertreated in older adults. A 2003 study of Medicare patients found that over 30% of those with depressive symptoms did not receive any treatment (Crystal, Sambamoorthi, Walkup, & Akincigil, 2003). Wittayanukorn, Qian, and Hansen (2014) found that, out of 1,177 individuals with clinically relevant depressive symptoms, approximately 70% did not receive any treatment and adults who were male, of Mexican American or African American ethnicity, and were 80 years or older were less likely to receive treatment. Additionally, a 2012 survey of 1,318 people aged 65 years and older that was conducted by the John A. Hartford Foundation found that an estimated 46% of the respondents received treatment for depression, but they reported not receiving follow-up care after treatment initiation (Langston, Undem, & Callahan, 2012). Primary care practitioners who typically care for older patients can only identify about half of adult patients suffering from depression. Moreover, many primary care practices do not have a trained staff member for mental health issues. The combination of these two factors can lead to inadequate treatment and maintenance of antidepressant therapy. This lack of treatment and diagnosis of depression results in poorer outcomes (Mulsant & Ganguli, 1999). Besides failure of recognition and treatment of depression in the primary care setting, public awareness of the serious health risks related to depression in later life has been low. The 2012 survey also found that 27% of the respondents believed that depression was part of the natural aging process, 21% of the respondents knew that depression increased risk of the development of dementia, and 34% understood that heart disease and depression were associated

(Langston et al., 2012). Another reason why depression is undertreated is stigma, since depression was once thought to be the result of psychological weakness.

Vascular depression hypothesis

Individuals with late-life depression are at elevated risk of CVD (Baldwin & O'Brien, 2002). Many studies recognize CVD predicts the onset of late-life depression, which is also itself an independent risk factor for development of coronary artery disease, stroke, and diabetes, whereas vascular disease contributes to the development of depression, coronary artery disease, stroke, and vascular dementia (Baldwin & O'Brien, 2002; Gorelick et al., 2011; Thomas, Kalaria, & O'Brien, 2004). The vascular depression hypothesis has been proposed to explain relationships between risk factors for cardiovascular disease and late-life depression (Alexopoulos, 2010; Alexopoulos et al., 1997; Taylor, Aizenstein, & Alexopoulos, 2013). Cardiovascular diseases are thought to lead to, exacerbate, or continue depression in older adults (Alexopoulos et al., 1997). Further investigation of the vascular depression hypothesis will contribute to ways of delaying or preventing cognitive decline and increased disability as the population ages.

Associations among subclinical cardiovascular disease, persistent depressive symptoms, mild cognitive impairment, and dementia

We hypothesize persistent depressive symptoms partially mediate the association of subclinical CVD with onset of mild cognitive impairment and dementia. Depression is considered a risk factor of dementia (Wint, 2011). Findings from a meta-analysis suggest people with late-life depression are at elevated risk of all-cause dementia, specifically

vascular dementia (Diniz et al., 2013). There have been few studies examining the temporal interplay of vascular disease, depression, mild cognitive impairment, and dementia longitudinally (Barnes et al., 2006; Barnes et al., 2012; Sheline et al., 2006). In one study that followed 2,220 participants for seven years, those with depressive symptoms at study initiation had a higher risk of developing Mild Cognitive Impairment than those without depressive symptoms (Barnes et al., 2006). Sheline et al. (2006) found that those with late-life depression had slowed processing speed and executive dysfunction, which operate through fronto-striatal disconnection. Vascular burden, depression severity, age, and education were associated with slowed processing speed (Sheline et al., 2006). Subclinical CVD is a strong predictor of clinical CVD (Chaves et al., 2004; Kuller et al., 2006; Kuller et al., 1995), so subclinical CVD may be associated with persistent depressive symptoms and cognitive impairment.

Associations among subclinical cardiovascular disease, depression, and mortality

Besides examining associations among subclinical CVD, persistent depressive symptoms, mild cognitive impairment, and dementia, we will examine the indirect effect of persistent depressive symptoms on the association between subclinical CVD and all-cause mortality. Severity of depression is a risk factor for all-cause mortality and cardiovascular-related mortality, and it is associated with cardiovascular risk factors (Ariyo et al., 2000; Schulz et al., 2000). Another risk factor for all-cause mortality is subclinical CVD (Kuller et al., 2006).

To our knowledge, only one study has examined whether depression plays a role in the association between CVD and all-cause mortality among community-dwelling

older adults. Almeida et al. (2012) examined whether depression modified the association between CVD and all-cause mortality. They reported that depression did not modify the association between CVD and all-cause mortality. Both depression and CVD each were independently associated with an elevated risk of death.

Study population

The target population is older adults living in the United States and countries similar to the United States who are at risk of developing cardiovascular disease and depression in the modern era. The source population is older adults living in the United States who are at risk of developing cardiovascular disease and depression in the modern era. The study population comes from the Johns Hopkins Precursors Study and the Cardiovascular Health Study.

Johns Hopkins Precursors Study. Caroline Bedell Thomas started the Johns Hopkins Precursors Study in 1947 by enrolling 1,337 students who matriculated into the graduating classes of 1948 to 1964 of The Johns Hopkins University School of Medicine. Participants have been followed regularly through annually mailed questionnaires since graduation, with an average response rate in over a five-year period of 90% (Gross et al., 2011). Self-reports of cardiovascular parameters have been found to be accurate (Klag et al., 1993).

Cardiovascular Health Study. The Cardiovascular Health Study is a community-based study of 5,888 men and women aged 65 years and older at baseline. The primary

objective was to assess risk factors for the development and progression of cardiovascular disease in older adults, which arose out of a dearth of data on risk factors in older adults (Fried et al., 1991). Participants were recruited from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania in 1989-1990. In 1992-1993, African American participants were actively recruited, and they comprise 15% of CHS participants. The eligibility criteria for both waves of enrollment were: 1) age 65 years or older; 2) not institutionalized; 3) expectation to stay in the current community for 3 or more years; 4) no active treatment for cancer; and 5) ability to provide informed consent without requiring a proxy respondent. Study visits occurred annually through 1998-1999 and telephone follow-up visits occur to present (Darsie et al., 2014). These study visits consisted of interviews, physical examinations, health questionnaires, and a fasting blood sample. Collection of hospital discharge summaries, and ICD-9 codes for all hospitalizations were collected during the follow-up period (Darsie et al., 2014). In 2005-2006, 1,677 of the remaining cohort agreed to participate in an in-person visit to evaluate physical and cognitive functioning (Jenny et al., 2011). The in-person visit consisted of updated medical history, medication inventory, social history, self-reported health, physical function (measured through self-report, isometric grip strength, and gait speed), physical activity, cognitive assessments, and a fasting blood sample (Jenny et al., 2011). Quality control procedures are described in Fried et al. (1991).

References

Alexopoulos, G.S. (2010). The vascular depression hypothesis: 10 years later. Biological Psychiatry, 60, 1304-1305.

Alexopoulos, G.S., Kiosses, D.N., Heo, M., Murphy, C.F., Shanmugham, B., & Gunning-Dixon, F. (2001). Executive dysfunction and the course of geriatric depression. *Biological Psychiatry*, 58, 204-210.

Alexopoulos, G.S., Meyers, B.S., Young, R.C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular Depression' Hypothesis. *Archives of General Psychiatry*, 54, 915-922.

Almeida, O.P., Alfonso, H., Flicker, L., Hankey, G.J., & Norman, P.E. (2012). Cardiovascular disease, depression and mortality: The Health in Men Study. *The American Journal of Geriatric Psychiatry*, 20(5), 433-440.

Ariyo, A.A., Haan, M., Tangen, C.M., Rutledge, J.C., Cushman, M., Dobs, A., . . . Cardiovascular Health Study Collaborative Research Group. (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. *Circulation*, 102, 1773-1779.

Baldwin, R.C. & O'Brien, J. (2002). Vascular basis of late-onset depressive disorder. *British Journal of Psychiatry*, 180, 157-160.

Barnes, D.E., Alexopoulos, G.S., Lopez, O.L., Williamson, J.D., & Yaffe, K. (2006). Depressive symptoms, vascular disease, and mild cognitive impairment: Findings from the Cardiovascular Health Study. *Archives of General Psychiatry*, 63(3), 273-279.

Barnes, D.E., Yaffe, K., Byers, A.L., McCormick, M., Schaefer, C., & Whitmer, R.A.

(2012). Mid-life versus late-life depressive symptoms and risk of dementia: differential effects for Alzheimer's disease and vascular dementia. *Archives of General Psychiatry*, 69(5), 493-498.

Becker, J.T., Lopez, O.L., Dew, M.A., Sweet, R.A., Chang, Y.F., Kuller, L.H., . . . Reynolds, C.F. (2009). Depressed mood is not a risk factor for incident dementia in a community-based cohort. *The American Journal of Geriatric Psychiatry*, 17, 653-663.

Chaves, P.H., Kuller, L.H., O'Leary, D.H., Manolio, T.A., Newman, A.B., & Cardiovascular Health Study. (2004). Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *American Journal of Geriatric Cardiology*, 13(3), 137-151.

Crystal, S., Sambamoorthi, U., Walkup, J.T., & Akincigil, A. (2003). Diagnosis and treatment of depression in the elderly Medicare population: predictors, disparities and trends. *Journal of American Geriatric Society*, 51, 1718-1728.

Darsie, B., Shlipak, M.G., Sarnak, M.J., Katz, R., Fitzpatrick, A.L., & Odden, M.C. (2014). Kidney function and cognitive health in older adults: The Cardiovascular Health Study. *American Journal of Epidemiology*, 180(1), 68-75.

Diniz, B.S., Butters, M.A., Albert, S.M., Dew, M.A., & Reynolds, C.F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry*, 202, 329-335.

Fried, L.P., Borhani, N.O., Enright, P., Furberg, C.D., Gardin, J.M., Kronmal, R.A., . . .

Weiler, P.G. (1991). The cardiovascular health study: design and rationale. *Annals of Epidemiology*, 1(3), 263-276.

Ganguli, M. (2009). Depression, cognitive impairment and dementia: Why should clinicians care about the web of causation? *Indian Journal of Psychiatry*, 51(Supplement 1), S29-S34.

García-Peña, C., Wagner, F.A., Sanchez-García, S., Espinel-Bermudez, C., Juarez-Cedillo, T., Perez-Zepeda, M., . . . Gallo, J.J. (2013). Late-life depressive symptoms: prediction models of change. *Journal of Affective Disorders*, 150, 886-894.

Gonzalez, H., Tarraf, W., Whitfield, K., & Gallo, J.J. (2012). Vascular depression prevalence and epidemiology in the United States. *Journal of Psychiatric Research*, 46(4), 456-461.

Gorelick, P.B., Scuteri, A., Black, S.E., DeCarli, C., Greenberg, S.M., Iadecola, C., . . . Seshadri, S. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 42, 2672-2713.

Gross, A.L., Rebok, G.W., Ford, D.E., Chu, A.Y., Gallo, J.J., Liang, K-Y, . . . Klag, M.J. (2011). Alcohol consumption and domain-specific cognitive function in older adults: longitudinal data from the Johns Hopkins Precursors Study. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, 66B(1), 39-47.

Jenny, N.S., French, B., Arnold, A.M., Strotmeyer, E.S., Cushman, M., Chaves, P.H.M., .

. . Newman, A.B. (2011). Long-term assessment of inflammation and healthy aging in late life: The Cardiovascular Health Study All Stars. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 67(9), 970-976.

Jorm, A.F. (2010). Is depression a risk factor for dementia or cognitive decline? *Gerontology*, 46, 219-227.

Klag, M.J., He, J., Mead, L.A., Ford, D.E., Pearson, T.A., & Levine, D.M. (1993). Validity of physicians' self-reports of cardiovascular disease risk factors. *Annals of Epidemiology*, 3(4), 442-447.

Kuller, L.H., Arnold, A.M., Psaty, B.M., Robbins, J.A., O'Leary, D.H., Tracy, R.P., . . . Chaves, P.H.M. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Archives of Internal Medicine*, 166(1), 71-78.

Kuller, L.H., Shemanski, L., Psaty, B.M., Borhani, N.O., Gardin, J., Haan, M.N., . . . Tracy, R. (1995). Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*, 92(4), 720-726.

Langston, C., Undem, T., & Callahan, C. (2012). *Silver and Blue: The Unfinished Business of Mental Health Care for Older Adults*: John A. Hartford Foundation.

Luchsinger, J.A., Reitz, C., Honig, L.S., Tang, M.X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*, 65(4), 545-551.

McDermott, L.M. & Ebmeier, K.P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, 119, 1-8.

Mulsant, B.H. & Ganguli, M. (1999). Epidemiology and diagnosis of depression in late life. *Journal of Clinical Psychiatry*, 60(suppl 20), 9-15.

Ortman, J.M., Velkoff, V.A., & Hogan, H. (2014). An aging nation: The older population in the United States. Washington, D.C.: U.S. Census Bureau.

Potter, G.G. & Steffens, D.C. (2007). Contribution of depression to cognitive impairment and dementia in older adults. *The Neurologist*, 13, 105-117.

Schulz, R., Beach, S.R., Ives, D.G., Martire, L.M., Ariyo, A.A., & Kop, W.J. (2000). Association between depression and mortality in older adults: The Cardiovascular Health Study. *Archives of Internal Medicine*, 160, 1761-1768.

Sheline, Y.I., Barch, D.M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., . . . Doraiswamy, P.M. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, 60, 58-65.

Steffens, D.C., Helms, M.J., Krishnan, K.R., & Burke, G.L. (1999). Cerebrovascular disease and depressive symptoms in the Cardiovascular Health Study. *Stroke*, 30, 2159-2166.

Steffens, D.C., Krishnan, K.R., Crump, C., & Burke, G.L. (2002). Cerebrovascular disease and evolution of depressive symptoms in the Cardiovascular Health Study. *Stroke*, 33, 1636-1644.

Taylor, W.D., Aizenstein, H.J., & Alexopoulos, G.S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, 18(9), 963-974.

Thomas, A.J., Kalaria, R.N., & O'Brien, J.T. (2004). Depression and vascular

disease: what is the relationship? *Journal of Affective Disorders*, 79, 81-95.

Wint, D. (2011). Depression: A shared risk factor for cardiovascular and Alzheimer disease. *Cleveland Clinic Journal of Medicine*, 78(S1), S44-S46.

Wittayanukorn, S., Qian, J., & Hansen, R.A. (2014). Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. *General Hospital Psychiatry*, 36, 330-336.

Cardiovascular Risk Factors and Risk of Incident Depression throughout Adulthood among Men: The Johns Hopkins Precursors Study

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Abstract

Introduction: Modifiable cardiovascular risk factors are associated with subsequent depression onset in older adults, but the effect of the timing of the cardiovascular risk factors occurring either before or after age 65 on incident depression is unclear.

Method: Participants were 1,190 male medical students without a diagnosis of depression, who matriculated between 1948 and 1964 and were followed through 2011. Cox Proportional Hazards models were used to assess the associations of vascular burden, diabetes, hypertension, hyperlipidemia, smoking status, and overweight/obese status with onset of adjudicated diagnosis of incident depression. Models were adjusted by race, enrollment wave, baseline age, physical activity, and heavy alcohol use.

Results: The analysis included 44,175 person-years of follow-up. Among participants who were depression-free up to age 65, vascular burden after age 65 (Hazard Ratio, [HR]: 2.13, 95% Confidence Interval, [CI]: 1.17, 3.90) was associated with onset of incident depression after age 65. The magnitude of vascular burden after age 65 is comparable to the effect of 8.2 additional years of age. Diabetes (HR: 2.79, 95% CI: 1.25, 6.26), hypertension (HR: 2.72, 95% CI: 1.52, 4.88), and hyperlipidemia (HR: 1.88, 95% CI: 1.05, 3.35) before age 65 were associated with incident depression after age 65. Men diagnosed with diabetes after age 65 had 2.87 times the risk of developing incident depression after age 65 (95% CI: 1.24, 6.62).

Conclusions: Results support the vascular depression hypothesis. Depression screening in older adults with vascular burden may prevent and treat late-onset depression.

Key Terms: vascular depression, depression, cardiovascular risk factors, hypertension, diabetes, hyperlipidemia

Introduction

Cardiovascular disease (CVD) is a common, growing public health challenge given increases in the older segments of the US population (Go et al., 2013). In 2013, 83.6 million Americans had one or more CVD, of whom 42.2 million were 60 years of age or older (Go et al., 2013). Prior research suggests CVD and depression have a reciprocal relationship: each increases the risk of developing the other (Alexopoulos, 2010; Alexopoulos et al., 1997; Barnes et al., 2012; Newberg, Davydow, & Lee, 2006). Despite being a top contributor to disability (García-Peña et al., 2013) and cognitive impairment (Diniz, Butters, Albert, Dew, & Reynolds, 2013), depression in older adults is often undertreated (Licht-Strunk, Beekman, de Haan, & van Marwijk, 2009).

The vascular depression hypothesis has been used to explain how CVD promulgates late-onset depression (Alexopoulos et al., 1997). Cardinal features of late-onset depression, here taken to indicate depression with incidence after age 65, are diagnosis of incident depression at age 65 and older and presence of vascular disease or cardiovascular risk factors (Alexopoulos et al., 1997). Secondary features include greater psychomotor disturbance, apathy, executive dysfunction, lesions in basal ganglia, and white matter hyperintensities (Thomas, Kalaria, & O'Brien, 2004). Modifiable cardiovascular risk factors include diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking (Barnes & Yaffe, 2011). The influence of cardiovascular risk factors on incident depression is likely more pronounced in older adults than in middle-aged or younger adults, due to underlying physiological mechanisms (Taylor, Aizenstein, & Alexopoulos, 2013).

Previous studies of associations of midlife cardiovascular risk factors and late-onset depression have used cohorts with short durations of follow-up or follow-up without repeated measurement of midlife cardiovascular risk factors (Barnes et al., 2012; Sheline et al., 2006). The present investigation addresses these limitations by leveraging high-quality prospectively collected data on cardiovascular risk factors and depression from a long-standing cohort with extensive follow-up. The study is well-suited to examine cardiovascular risk factors occurring before vs. after age 65 and diagnosis of incident depression.

We evaluated the timing during life of the occurrence of modifiable cardiovascular risk factors and determined the extent to which they are associated with subsequent development of incident depression. Pursuant to the vascular depression hypothesis, we hypothesized vascular burden and cardiovascular risk factors occurring before age 65 are associated with increased risk of developing incident depression after age 65, not before age 65. We examined this hypothesis using data up to age 65 to examine the association of cardiovascular risk factors with incident depression before age 65. Among participants who survived depression-free up to age 65, we determined whether the presence of cardiovascular risk factors occurring before vs. after age 65 was associated with onset of incident depression after age 65 (Figure 1).

Methods

The Johns Hopkins Precursors Study

The Johns Hopkins Precursors Study, initiated in 1946, enrolled 1,337 medical school students in matriculating classes from 1948-1964 of The Johns Hopkins School of Medicine. Participants are followed approximately annually through mailed questionnaires to update morbidity and exposure information (Figure 2). The average 5-year period response rate is 90% (range 87% to 94%). Vital status is known for over 99% of the cohort. Self-reports of body mass index (BMI) and systolic blood pressure (SBP) have been validated externally (Klag et al., 1993). Study procedures are reviewed regularly and approved by the Johns Hopkins University School of Medicine Institutional Review Board.

We aimed to examine incident depression, hence excluded participants diagnosed with clinical depression before graduating from medical school (N=16), and those with no follow-up (N=9). The final sample size for this study was N=1,190 participants.

Incident Depression

The primary outcome was first diagnosis of depression. Participants or family members submitted approximately annually mailed questionnaires inquiring about medical and psychiatric conditions in a checklist (Chang, Ford, Mead, Cooper-Patrick, & Klag, 1997; Ford et al., 1998). Also, they answered questions about use of antidepressant

medication multiple times and lifetime history of receiving care from a mental health specialist for an emotional problem in 1988 (Chang et al., 1997; Ford et al., 1998). Depression before medical school graduation were ascertained by history and physical examination, review of student health records for information about treatment and hospitalization for depression, and exit interviews with specific questions about depressive symptoms. Those who committed suicide were included in the case definition of depression.

Additionally, a committee of physician reviewers, unaware of the study's hypothesis, adjudicated diagnoses alongside age of onset after reviewing participant self-reports (Chang et al., 1997; Ford et al., 1998). Strict adherence to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition was not possible, so the term, major depression, is not used. Questions about depression treatment assessed validity of the diagnosis of clinical depression (Chang et al., 1997; Ford et al., 1998).

Vascular Burden

Vascular burden was defined by an adapted version of the Framingham CVD Risk Score (FCRS). FCRS is validated in participants aged 30-74 years without CVD, so we calculated scores within that age range (Cook et al., 2012; D'Agostino et al., 2008). The adapted version of the FCRS incorporates current smoking status, BMI, age, diabetes, and treated or untreated SBP (Cook et al., 2012). We used this version, since data for total and HDL cholesterol were unavailable for most visits. We assumed participants

diagnosed as hypertensive were treated for hypertension because diagnostic criteria for hypertension in the study included drug therapy (Wang et al., 2008).

Cardiovascular Risk Factors

Cardiovascular risk factors were time-varying diabetes, hypertension, hyperlipidemia, overweight/obese status, and ever smoking status. Figure 2 provides the data collection schedule of these risk factors. Participants reported age and year of onset of diabetes, hypertension, and hyperlipidemia, which were confirmed by an adjudication committee. Overweight/obesity status was defined at each study interval by a cut-off of BMI≥25 kg/m2 (Barone et al., 2006). For ever-smoking status, participants were classified as current/former smokers or never smokers in each year of follow-up (Figure 2).

Covariates

All models were adjusted by white race, baseline age, enrollment cohort (1957-1964 vs. 1948-1956), heavy alcohol use (daily/almost daily vs. less than daily) and physical activity (none vs. some) at baseline and age 65.

Analytic Strategy

We characterized the sample using means and percentages at baseline and age 65. Using Kaplan-Meier analysis, we compared the incidence of clinical depression developing at age 65 and older for time-invariant versions of each cardiovascular risk factor prior to age 65 (Kaplan & Meier, 1958). The difference in depression incidence between ever having and never having each cardiovascular risk factor before age 65 was tested using log-rank tests (Peto & Peto, 1972). This approach enabled us to assess whether the presence of cardiovascular risk factors before age 65 contributes to risk for incident depression after age 65.

We compared the incidence of depression before and after age 65 using discrete-time Cox proportional hazards survival models (Cox, 1972; Prentice & Gloeckler, 1978). We first modeled associations of time-varying indicators for vascular burden and cardiovascular risk factors occurring before age 65 with incident depression before age 65 (dotted line in Figure 1). We did not anticipate strong associations, since the vascular depression hypothesis posits association of cardiovascular risk factors with depression onset in late life. We tested the proportional hazards assumption through log-log plots (Cox, 1972).

Next, we modeled associations of time-varying indicators of vascular burden and cardiovascular risk factors occurring before and after age 65 with incident depression at age 65 or older using the subset that survived depression-free until age 65 (solid lines in Figure 1). In other models to tease apart the timing of the onset of vascular burden and each cardiovascular risk factor on risk for incident depression, we used a three-level time-varying indicator for each cardiovascular risk factor: (1) newly occurred at age 65 or older, (2) newly occurred before age 65, and (3) never occurred as the reference group.

Hazard ratios and 95% confidence intervals for associations were estimated using discrete-time Cox proportional hazards models (Cox, 1972; Prentice & Gloeckler, 1978). Participants contributed time from age at graduation from medical school until age of incident depression, censoring due to loss to follow-up or death, or age of administrative censoring in 2011.

FCRS was standardized to two standard deviations of the baseline distribution to place effect estimates on approximately the same scale as those for the binary CVD indicators (Gelman, 2008). To assist clinical interpretation, we divided the hazard for vascular burden by the coefficient for baseline age to estimate how much older a person would have to be at baseline to have the same magnitude of risk for incident depression. Statistical significance was defined by $\alpha<0.05$. Analyses were conducted using STATA 13.1 (StataCorp, 2013).

Sensitivity Analysis

To examine potential reverse causation, we calculated percentages of those who switched cardiovascular risk factor status from absence to presence and vice versa prior to one-year of incident depression. We excluded these participants with potential co-occurring events to see if inferences changed. To evaluate the robustness of our findings for the selected age cutoff, we repeated the analysis using ages 70 and 75 instead of age 65. To evaluate the potential for death being responsible for associations with cardiovascular risk factors instead of depression, we used competing-risks regression based on proportional sub-hazards model to examine the association of cardiovascular

risk factors with onset of death before incident depression (Fine & Gray, 1999). Despite small sample size, we repeated statistical analyses in women to evaluate robustness of associations by sex.

Results

Sample Characteristics

Table 1 shows sample characteristics of 1,171 white and 19 non-white male participants at baseline (medical school graduation) and at age 65. Mean age at graduation from medical school was 26.3 years (standard deviation, [SD]=2.3 years). Fifty-two percent of the sample enrolled between 1948 and1956 (Table 1). Mean SBP rose from 116.0 mmHg (SD=9.3 mmHg) at baseline to 127.6 mmHg (SD=13.7 mmHg) at age 65. The number of cases of diabetes, hypertension, and hyperlipidemia increased between baseline and age 65 (Table 1). Mean BMI was 23.1 kg/m^2 (SD=2.6 kg/m^2) at baseline and 25.0 kg/m^2 (SD=3.4 kg/m^2) at age 65. There were 556 (50.9%) current smokers at baseline and 60 (9.9%) at age 65 (Table 1).

There were 265 cases of incident depression (mean age of diagnosis = 57.1 years [SD=14.7 years]). The incidence of depression was 22.3% in the overall sample, 14.7% (n=175) before age 65 (N=1,190), and 11.0% (n=90) at age 65 and older (N=821). Among participants who died before age 65 (n=134, 11.3%), 28 (20.9%) had incident depression. Among participants who died after age 65 (n=321, 27.0%), 88 (27.4%) had incident depression.

Cardiovascular Risk Factors and Depression up to Age 65

Using data up to age 65, participants contributed 38,825 person-years between baseline and onset of incident depression or age 65 (median 56 years). Table 2 shows unadjusted and adjusted hazard ratios for associations of vascular burden and cardiovascular risk factors with onset of incident depression up to age 65. After adjustment, vascular burden before age 65 was not associated with onset of incident depression up to age 65 (Hazard Ratio [HR]:0.84, 95% Confidence Interval [CI]: 0.59, 1.21) (Table 2, top row). Overweight/obese men had 0.62 times the risk of depression before age 65 than men of normal BMI (95% CI: 0.42, 0.93). No other associations between cardiovascular risk factors and onset of incident depression up to age 65 were appreciably greater than null.

Cardiovascular Risk Factors and Depression among Those Depression-Free to Age 65

Figure 3 shows Kaplan-Meier survival curves comparing risk of incident depression diagnosed after age 65 between the group with a cardiovascular risk factor before age 65 vs. those who did not. Participants who survived depression-free up to age 65 contributed 44,175 person-years between baseline and onset of incident depression, death, or end of follow-up in 2011.

Table 3 shows adjusted hazard ratios for the associations of vascular burden and cardiovascular risk factors present before vs. after age 65 with onset of incident depression among those who never developed depression prior to age 65. Analyses were adjusted for baseline age, enrollment wave, physical activity at age 65 and alcohol use at age 65. Vascular burden level after age 65 (HR: 2.13, 95% CI: 1.17, 3.90) were

associated with onset of incident depression after age 65 (Table 3, top row). To provide context for this finding, we used the coefficient for baseline age in the hazards model to estimate how much older, on average, a person would be to have the same magnitude of elevated risk of incident depression for vascular burden. Among persons aged 65 and older, the elevated hazard of incident depression associated with a two SD higher vascular burden after age 65 is equivalent to being 8.2 years older.

Men with diabetes diagnosed before age 65 had 2.79 times the risk of developing incident depression after age 65 than those without diabetes (95% CI: 1.25, 6.26) after adjustment (Table 3). The same was true of hypertension (HR: 2.72, 95% CI: 1.52, 4.88) and hyperlipidemia (HR: 1.88, 95% CI: 1.05, 3.35). Men diagnosed with diabetes after age 65 had 2.87 times the risk of developing incident depression after age 65 than men without diabetes (95% CI: 1.24, 6.62) after adjustment (Table 3). No other cardiovascular risk factor after age 65 was associated with onset of incident depression.

Sensitivity Analysis

Within one year of onset of incident depression (N=264, 22.5% of the sample), 3 (1.1%) started or stopped smoking, 22 (8.3%) developed diabetes, 6 (2.3%) developed hyperlipidemia, 0 (0.0%) experienced an increase in BMI to 25 kg/m^2 or greater, and 20 (7.6%) developed hypertension. Inferences did not change after excluding these participants.

The adjusted sub-hazard ratios of associations of cardiovascular risk factors with onset of death before incident depression in both subsets are shown in Table 4 and Table

5. Among the overall cohort, cardiovascular risk factors were not associated with death more than depression up to age 65 ($p > 0.05$) (Table 4). Among the subset, diabetes before age 65 (Subhazard Ratio [SHR]=2.14, 95% CI: 1.17, 3.91) and ever smoking status after age 65 (SHR=2.23, 95% CI: 1.26, 3.91) were associated more with death than depression after age 65 (Table 5).

Associations for women were in similar directions as those for men, although associations among women did not reach statistical significance (Table 6 & Table 7). Results were similar when using ages 70 and 75 as cutoffs (Table 8 & Table 9).

Discussion

In this longitudinal study of adults followed for up to 63 years after medical school, vascular burden and specifically, diabetes, hypertension, and hyperlipidemia were associated with increased risk of onset of incident depression among men who survived depression-free to age 65. Vascular burden accelerates onset of incident depression, since the magnitude of vascular burden after age 65 is comparable to the effect of 8.2 additional years of age. Vascular burden and cardiovascular risk factors, except for overweight/obese status, were not associated with onset of incident depression developing before age 65. These findings are consistent with the premise of the vascular depression hypothesis that cardiovascular risk factors may underlie depression in adults over age 65 (Alexopoulos et al., 1997).

Our study is broadly concurrent with past work distinguishing early-onset depression and late-onset depression pursuant to the vascular depression hypothesis (Bukh, Bock, Vinberg, Gether, & Kessing, 2011). There is substantial research suggesting greater roles medical and cardiovascular comorbidity in late-onset depression characterized as an initial depressive episode occurring later in life. Our study moves this research area by distinguishing between midlife and later-life cardiovascular risk factors.

The vascular depression hypothesis implies accumulation of small-vessel disease could compromise the integrity of subcortical regions of the brain involved in mood regulation (Taylor et al., 2013). Modifiable cardiovascular risk factors are associated with small-vessel brain disease (Taylor et al., 2013). As vascular burden increases with increasing age, small-vessel brain disease could accumulate, thus elevating the risk of the onset of clinical depression in older adults. Taylor et al. (2013) proposed that pro-

inflammatory processes contribute to acceleration of vascular damage and deficits in perfusion, resulting in white matter lesions that disrupt structural and functional connectivity. Pro-inflammatory states arise in aging and chronic disease via cardiovascular risk factors.

Previous studies with shorter follow-up of one to two years have provided evidence in support of the vascular depression hypothesis, but none have examined these relationships throughout the life course as our study did (Lyness, King, Conwell, Cox, & Caine, 2000; Mast, Neufeld, MacNeill, & Lichtenberg, 2004). Unlike previous studies of one cardiovascular risk factor (e.g., diabetes (Mezuk, Eaton, Albrecht, & Golden, 2008), hypertension (Meyer, Armenian, Eaton, & Ford, 2004), hyperlipidemia (Chuang et al., 2014), and smoking status (Pasco et al., 2008)), the present study examined vascular burden and cardiovascular risk factors. Epidemiologic studies with incident cases of depression are rare, and the long-term follow-up of a single cohort confers a considerable advantage by sharpening the focus on the temporal relationship between the cardiovascular risk factors and lifetime depression onset.

We found an inverse association between overweight status and depression before age 65 among men. Evidence of an association between overweight status and depression has been mixed in other longitudinal studies (Palinkas, Wingard, & Barrett-Connor, 1996; Roberts, Kaplan, Shema, & Strawbridge, 2000; Shelton & Miller, 2010). One potential biological mechanism is that carbohydrate cravings may temporarily relieve depressive symptoms via increased serotonergic activity (Lieberman, Wurtman, & Chew, 1986). Further, we found a positive association between hyperlipidemia and depression onset after age 65, consistent with previous research (Chuang et al., 2014).

Our study has considerable strengths. The Johns Hopkins Precursors Study is a prospective cohort study with lengthy follow-up, high response rates, and repeated measurement of cardiovascular risk factors (Chang et al., 1997; Ford et al., 1998; Wang et al., 2008). One strength is the sample consists of former medical students who became physicians, likely increasing the accuracy of self-reported conditions, and the same participants are followed prospectively (Chang et al., 1997; Ford et al., 1998; Wang et al., 2008). Although the case definition for depression may have been more reliable if standard criteria were applied retrospectively, it would do so at the expense of validity if the presentation of depression changes with age. While new cases of depression identified in older age might be the most severe cases, if the participants reporting depression in later life were the most severe cases, then one would expect these participants would have reported depression earlier in life, not only in old age. Another advantage is the validity of self-reported cardiovascular risk factors compared to in-person measures, thereby ensuring minimal bias (Klag et al., 1993).

Several caveats of the study should be mentioned. Incidences of depression in our study are not comparable to nationally representative estimates because we excluded cases occurring before graduation, leading to lower incidence before age 65 than national estimates (Kessler & Wang, 2008). Additionally, physicians have higher rates of depression than the general population, thus the overall incidence rate in our sample of 22.3% is slightly higher than national estimates of 16.6% (Kessler & Wang, 2008).

Another caveat is other variables not incorporated into the analyses, i.e., genes and anxiety, could bias associations. We did not adjust models for mental status because medical school graduates are likely to perform at ceiling on screening tools developed to

detect dementias later in the life course. Selection factors could also affect our study's generalizability; particularly, high socioeconomic status could have a protective effect against depression, thus leading to a potentially conservative estimate of risk related to depression (Ford et al., 1998). This limitation is also an advantage because the sample's homogeneity and selectivity ensures fewer unknown confounders. A third limitation is the small sample size and limited number of cases especially in the under-65 analysis, resulting in wide confidence intervals. Fourth, some participants (11%) died before age 65, thus death is a potentially competing outcome with depression after age 65 although sensitivity analyses showed no cardiovascular risk factors are associated with death prior to depression before age 65. A final limitation is that the sample and thus inferences are restricted to men. In a sensitivity analysis we repeated analyses in women; although associations were similar in magnitude, we were unable to conclude comparable relationships in women, due to limited sample size.

Depression is under-detected by primary care physicians (Licht-Strunk et al., 2009), yet related to earlier risk of disability and cognitive impairment (Diniz et al., 2013; García-Peña et al., 2013). The predictive associations of modifiable cardiovascular risk factors and vascular burden with onset of incident depression are consistent with the vascular depression hypothesis, and underscore the need to screen older adults with multiple cardiovascular risk factors for depressive symptoms. Depressive care management can reduce depressive symptoms, increase quality of life, increase antidepressant treatment adherence, decrease hospitalizations, and extend life (Gallo et al., 2013; Unutzer et al., 2002).

References

Alexopoulos, G. S. (2010). The vascular depression hypothesis: 10 years later. *Biological Psychiatry*, 60, 1304-1305.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular Depression' Hypothesis. *Archives of General Psychiatry*, 54, 915-922.

Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology*, 10, 819-828.

Barnes, D. E., Yaffe, K., Byers, A. L., McCormick, M., Schaefer, C., & Whitmer, R. A. (2012). Midlife vs. late-life depressive symptoms and the risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Archives of General Psychiatry*, 69(5), 493-498.

Barone, B. B., Clark, J. M., Wang, N.-Y., Meoni, L. A., Klag, M. J., & Brancati, F. L. (2006). Lifetime weight patterns in male physicians: the effects of cohort and selective survival. *Obesity*, 14(5), 902-908. doi:10.1038/oby.2006.104

Bukh, J. D., Bock, C., Vinberg, M., Gether, U., & Kessing, L. V. (2011). Differences between early and late onset adult depression. *Clinical Practice and Epidemiology in Mental Health*, 7, 140-147. doi:10.2174/1745017901107010140

Chang, P. P., Ford, D. E., Mead, L. A., Cooper-Patrick, L., & Klag, M. J. (1997). Insomnia in young men and subsequent depression: The Johns Hopkins Precursors Study. *American Journal of Epidemiology*, 146(2), 105-114.

Chuang, C.-S., Yang, T.-Y., Muo, C.-H., Su, H.-L., Sung, F.-C., & Kao, C.-H. (2014).

Hyperlipidemia, statin use and the risk of developing depression: a nationwide retrospective cohort study. *General Hospital Psychiatry*, 36(5), 497-501.

Cook, N. R., Paynter, N. P., Eaton, C. B., Manson, J. E., Martin, L. W., Robinson, J. G., . . . Ridker, P. M. (2012). Comparison of the Framingham and Reynolds risk scores for global cardiovascular risk prediction in the Multiethnic Women's Health Initiative. *Circulation*, 125(14), 1748-1756.

Cox, D. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society, Series B*, 34, 187-220.

D'Agostino, R., Vasan, R., Pencina, M., Wolf, P., Cobain, M., Massaro, J., & Kannel, W. (2008). General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation*, 117(6), 743-753.

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry*, 202, 329-335.

Fine, J., & Gray, R. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of American Statistical Association*, 94, 496-509.

Ford, D., Mead, L., Chang, P., Cooper-Patrick, L., Wang, N., & Klag, M. (1998). Depression is a risk factor for coronary artery disease in men: The Precursors Study. *Archives of Internal Medicine*, 158(13), 1422-1426.

Gallo, J., Morales, K., Bogner, H., Raue, P., Zee, J., Bruce, L., & Reynolds, C. (2013).

Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. *BMJ*, 346, f2570. doi:10.1136/bmj.f2570

García-Peña, C., Wagner, F. A., Sanchez-García, S., Espinel-Bermudez, C., Juarez-Cedillo, T., Perez-Zepeda, M., . . . Gallo, J. J. (2013). Late-life depressive symptoms: Prediction models of change. *Journal of Affective Disorders*, 150, 886-894.

Gelman, A. (2008). Scaling regression inputs by dividing by two standard deviations. *Statistics in Medicine*, 27, 2865-2873.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2013). Heart disease and stroke statistics - 2013 update: A report from the American Heart Association. *Circulation*, 127, e6-e245.

Kaplan, E., & Meier, P. (1958). Non-parametric estimation from incomplete observations. *Journal of American Statistical Association*, 53, 457-481.

Kessler, R., & Wang, P. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annual Review of Public Health*, 29, 115-129.

Klag, M. J., He, J., Mead, L. A., Ford, D. E., Pearson, T. A., & Levine, D. M. (1993). Validity of physicians' self-reports of cardiovascular disease risk factors. *Annals of Epidemiology*, 3(4), 442-447.

Klag, M. J., Wang, N.-Y., Meoni, L. A., Brancati, F. L., Cooper, L. A., Liang, K.-Y., . . .

Ford, D. E. (2002). Coffee intake and risk of hypertension: The Johns Hopkins Precursors Study. *Archives of Internal Medicine*, 162, 657-662.

Licht-Strunk, E., Beekman, A. T. F., de Haan, M., & van Marwijk, H. W. (2009). The prognosis of undetected depression in older general practice patients: a one year follow-up study. *Journal of Affective Disorders*, 114, 310-315.

Lieberman, H., Wurtman, J., & Chew, B. (1986). Changes in mood after carbohydrate consumption among obese individuals. *The American Journal of Clinical Nutrition*, 44(6), 772-778.

Lyness, J. M., King, D. A., Conwell, Y., Cox, C., & Caine, E. D. (2000). Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *American Journal of Psychiatry*, 157(9), 1499-1501.

Mast, B. T., Neufeld, S., MacNeill, S. E., & Lichtenberg, P. A. (2004). Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *The American Journal of Geriatric Psychiatry*, 12, 93-101.

Meyer, C., Armenian, H., Eaton, W., & Ford, D. (2004). Incident hypertension associated with depression in the Baltimore Epidemiologic Catchment area follow-up study. *Journal of Affective Disorders*, 83(127-133).

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*, 31(12), 2383-2390.

Newberg, A., Davydow, D., & Lee, H. (2006). Cerebrovascular disease basis of depression: post-stroke depression and vascular depression. *International Review of Psychiatry*, 18(5), 433-441.

Palinkas, L. A., Wingard, D. L., & Barrett-Connor, E. (1996). Depressive symptoms in

overweight and obese older adults: a test of the "jolly fat" hypothesis. *Journal of Psychosomatic Research*, 40(1), 59-66.

Pasco, J. A., Williams, L. J., Jacka, F. N., Ng, F., Henry, M. J., Nicholson, G. C., . . . Berk, M. (2008). Tobacco smoking as a risk factor for major depressive disorder: population-based study. *The British Journal of Psychiatry*, 193(4), 322-326.

Peto, R., & Peto, J. (1972). Asymptotically efficient rank invariant test procedures. *Journal of the Royal Statistical Society, Series B*, 135(185-198).

Prentice, R., & Gloeckler, L. (1978). Regression analysis of grouped survival data with application to breast cancer data. *Biometrics*, 34(1), 57-67.

Roberts, R. E., Kaplan, G. A., Shema, S. J., & Strawbridge, W. J. (2000). Are the obese at greater risk for depression? *American Journal of Epidemiology*, 152(2), 163-170.

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., . . . Doraiswamy, P. M. (2006). Cognitive function in late life depression: Relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, 60(1), 58-65.

Shelton, R. C., & Miller, A. H. (2010). Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. *Progress in Neurobiology*, 91(4), 275-299.

StataCorp. (2013). *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

Taylor, W., Aizenstein, H., & Alexopoulos, G. S. (2013). The vascular depression

hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, 18, 963-974.

Thomas, A. J., Kalaria, R. N., & O'Brien, J. T. (2004). Depression and vascular disease: What is the relationship? *Journal of Affective Disorders*, 79, 81-95.

Unutzer, J., Katon, W., Callahan, C., Jr., J. W., Hunkeler, E., Harpole, L., . . . IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. (2002). Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA*, 288(22), 2836-2845.

Wang, N.-Y., Young, J. H., Meoni, L. A., Ford, D. E., Erlinger, T. P., & Klag, M. J. (2008). Blood pressure change and risk of hypertension associated with parental hypertension. *Archives of Internal Medicine*, 168(6), 643-648.

Table 1. Comparison of male participants at baseline and age 65 from the Johns Hopkins Precursors Study (1947-2011).

Characteristics	**Baseline n=1,190**	**Age 65 n=821**
Age at Graduation, mean (SD)	26.3 (2.3)	---
Enrollment Wave		
1948-1956	623 (52.4)	---
1957-1964	567 (47.7)	---
Total Cholesterol, mean (SD), mg/dL	192.4 (29.2)	---
Systolic Blood Pressure, mean (SD), mm Hg	116.0 (9.3)	127.6 (13.7)
Diabetes, n (%)	6 (0.6)	50 (8.2)
Hypertension, n (%)	28 (2.6)	253 (41.2)
Hyperlipidemia, n (%)	94 (8.7)	251 (40.6)
BMI, mean (SD), kg/m^2	23.1 (2.6)	25.0 (3.4)
Current Smoker, n (%)	556 (50.9)	60 (9.9)
Lack of Physical Activity, n (%)	501 (50.5)	258 (32.7)
Heavy Alcohol Use, n (%)	87 (8.3)	161 (19.2)
Caucasian, n (%)	1,171 (98.4)	---

P-values based on chi-squared tests and t-tests. Tabulated values are means with standard deviations in parentheses, except where noted. mg/dL=milligrams per deciliter; mm Hg=millimeters of mercury; kg/m^2=kilograms per meters-squared

Table 2. Associations of vascular burden and cardiovascular risk factors with incident clinical depression before age 65 (N=1,190). Data from the Johns Hopkins Precursors Study (1947-2011).

	Unadjusted		Adjusted[+]	
Cardiovascular Risk Factors	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Vascular burden (FCRS)	0.83	(0.59, 1.15)	0.84	(0.59, 1.21)
Diabetes	0.93	(0.34, 2.51)	1.00	(0.37, 2.73)
Hypertension	1.06	(0.70, 1.61)	1.01	(0.64, 1.60)
Hyperlipidemia	1.02	(0.68, 1.54)	0.80	(0.50, 1.27)
Overweight or Obese Status**	0.78	(0.55, 1.11)	0.62*	(0.42, 0.92)
Ever Smoking Status	0.89	(0.65, 1.21)	0.87	(0.61, 1.23)

*P<0.05 **Overweight or obese defined as 25kg/m^2 or greater. [+]Adjusted by race, baseline age, enrollment wave, baseline lack of physical activity, and baseline heavy alcohol use. FCRS = Framingham Cardiovascular Disease Risk Score

This analysis refers to the dotted line in Figure 1. The hazard ratio associated with the FCRS represents a 2 standard deviation difference in score. The reference for individual conditions is never having the cardiovascular risk factor.

Table 3. Associations of vascular burden and cardiovascular risk factors with incident clinical depression after age 65 (N=821). Data from the Johns Hopkins Precursors Study (1947-2011).

	Occurrence of cardiovascular risk factors before age 65 Vs. Never		Occurrence of cardiovascular risk factors at age 65 and older Vs. Never	
Cardiovascular Risk Factors	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Vascular Burden (FCRS)	1.78	(0.22, 14.44)	2.13*	(1.17, 3.90)
Diabetes	2.79*	(1.25, 6.26)	2.87*	(1.24, 6.62)
Hypertension	2.72*	(1.52, 4.88)	2.01	(0.87, 4.60)
Hyperlipidemia	1.88*	(1.05, 3.35)	1.48	(0.69, 3.19)
Overweight or Obese Status**	1.33	(0.76, 2.33)	1.46	(0.42, 5.09)
Ever Smoking Status	1.02	(0.26, 3.96)	1.35	(0.77, 2.38)

*Statistically significant at $P \leq 0.05$. **Overweight or obese defined as 25kg/m^2 or greater. All analyses were adjusted by race, baseline age, enrollment wave, lack of physical activity at age 65, and heavy alcohol use at age 65.

FCRS = Framingham Cardiovascular Disease Risk Score

This analysis refers to the two solid lines in Figure 1. The hazard ratio associated with the FCRS represents a 2 standard deviation difference in score. The reference for individual conditions is never having the cardiovascular risk factor.

Table 4. Competing risk analysis using incident clinical depression as a competing risk for death and associations with cardiovascular risk factors after covariate adjustment (N=1,190). Data from the Johns Hopkins Precursors Study (1947-2011).

Cardiovascular Risk Factors	Adjusted[+] Subhazard Ratios	95% CI
Diabetes	---	---
Hypertension	1.65	(0.34, 8.08)
Hyperlipidemia	0.45	(0.07, 2.95)
Overweight/Obese	2.97	(0.83, 10.61)
Ever Smoking Status	2.46	(0.66, 9.19)

CI = Confidence Interval

[+]Adjusted by race, baseline age, enrollment wave, baseline physical activity, and baseline heavy alcohol use.

Note: There were 28 participants who died, and 134 competing events of depression before death.

Table 5. Competing risk analysis using incident clinical depression as a competing risk of death and associations with cardiovascular risk factors after covariate adjustment (N=821). Data from the Johns Hopkins Precursors Study (1947-2011).

	Occurrence of Cardiovascular Risk Factor Before Age 65 Vs. Never		**Occurrence of Cardiovascular Risk Factor at Age 65 & Older Vs. Never**	
Cardiovascular Risk Factors	**Adjusted[+] Subhazard Ratios**	**95% CI**	**Adjusted[+] Subhazard Ratios**	**95% CI**
Diabetes	2.14*	(1.17, 3.91)	1.61	(0.83, 3.14)
Hypertension	1.33	(0.85, 2.08)	0.78	(0.45, 1.39)
Hyperlipidemia	0.68	(0.42, 1.10)	0.69	(0.41, 1.17)
Overweight/Obese	1.64*	(1.03, 2.60)	1.15	(0.45, 2.90)
Ever Smoking Status	0.98	(0.16, 6.16)	1.79*	(1.15, 2.77)

*P<0.05, CI = Confidence Interval

[+]Adjusted by race, baseline age, enrollment wave, physical activity at age 65, and heavy alcohol use at age 65

Note: There were 145 individuals who died after age 65, and there were 38 competing events of depression before death.

Table 6. Differences in the associations of vascular burden and cardiovascular risk factors with incident clinical depression before age 65 between men (N=1,190) and women (N=118). Data from the Johns Hopkins Precursors Study (1947-2011).

	Females				Males			
	Unadjusted		Adjusted+		Unadjusted		Adjusted+	
Cardiovascular Risk Factors	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Vascular burden (FCRS)	1.03	(0.33, 3.27)	0.77	(0.19, 3.11)	0.83	(0.59, 1.15)	0.84	(0.59, 1.21)
Diabetes	---	---	---	---	0.93	(0.34, 2.51)	1.00	(0.37, 2.73)
Hypertension	0.55	(0.07, 4.53)	0.93	(0.10, 8.68)	1.06	(0.70, 1.61)	1.01	(0.64, 1.60)
Hyperlipidemia	---	---	---	---	1.02	(0.68, 1.54)	0.80	(0.50, 1.27)
Overweight or Obese Status**	---	---	---	---	0.78	(0.55, 1.11)	0.62*	(0.42, 0.92)
Ever Smoking Status	1.32	(0.48, 3.63)	1.39	(0.43, 4.50)	0.89	(0.65, 1.21)	0.87	(0.61, 1.23)

**Overweight or obese defined as 25kg/m^2 or greater. +Adjusted by race, baseline age, enrollment wave, baseline physical activity, and baseline heavy alcohol use. FCRS = Framingham Cardiovascular Disease Risk Score

This analysis refers to the dotted line in Figure 1. The hazard ratio associated with the FCRS represents a 2 standard deviation difference in score. The reference for individual conditions is never having the cardiovascular risk factor.

Table 7. Differences in the associations of vascular burden and cardiovascular risk factors with incident clinical depression after age 65 between men (N=821) and women (N=75). Data from the Johns Hopkins Precursors Study (1947-2011).

	Females				Males			
	Occurrence of cardiovascular risk factors before age 65 Vs. Never		Occurrence of cardiovascular risk factors at age 65 and older Vs. Never		Occurrence of cardiovascular risk factors before age 65 Vs. Never		Occurrence of cardiovascular risk factors at age 65 and older Vs. Never	
Cardiovascular Risk Factors	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Vascular Burden (FCRS score)	---	---	---	---	1.78	(0.22, 14.44)	2.13*	(1.17, 3.90)
Diabetes	---	---	---	---	2.79*	(1.25, 6.26)	2.87*	(1.24, 6.62)
Hypertension	2.84	(0.15, 52.72)	2.45	(0.14, 43.35)	2.72*	(1.52, 4.88)	2.01	(0.87, 4.60)
Hyperlipidemia	3.47	(0.15, 78.74)	3.60	(0.19, 67.48)	1.88*	(1.05, 3.35)	1.48	(0.69, 3.19)
Overweight or Obese Status	---	---	---	---	1.33	(0.76, 2.33)	1.46	(0.42, 5.09)
Ever Smoking Status	---	---	0.87	(0.07, 10.54)	1.02	(0.26, 3.96)	1.35	(0.77, 2.38)

*Statistically significant at P≤ 0.05. **Overweight or obese defined as 25kg/m^2 or greater. All analyses were adjusted by race, baseline age, enrollment wave, physical activity at age 65, and heavy alcohol use at age 65. FCRS = Framingham Cardiovascular Disease Risk Score

This analysis refers to the two solid lines in Figure 1. The hazard ratio associated with the FCRS represents a 2 standard deviation difference in score. The reference for individual conditions is never having the cardiovascular risk factor.

Table 8. Differences in the associations of vascular burden and cardiovascular risk factors with incident clinical depression before ages 70 and 75 among men (N=1,190). Data from the Johns Hopkins Precursors Study (1947-2011).

	Cutoff of Age 70				Cutoff of Age 75			
	Unadjusted		Adjusted[+]		Unadjusted		Adjusted[+]	
Cardiovascular Risk Factors	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Vascular burden (FCRS)	1.04	(0.78, 1.39)	1.04	(0.76, 1.43)	1.15	(0.88, 1.51)	1.11	(0.83, 1.50)
Diabetes	1.62	(0.85, 3.09)	1.46	(0.71, 3.01)	1.88*	(1.10, 3.20)	1.81	(0.99, 3.28)
Hypertension	1.31	(0.92, 1.86)	1.25	(0.84, 1.84)	1.34	(0.97, 1.85)	1.24	(0.86, 1.78)
Hyperlipidemia	1.04	(0.73, 1.49)	0.92	(0.61, 1.37)	1.10	(0.80, 1.53)	1.02	(0.71, 1.47)
Overweight or Obese Status**	0.82	(0.59, 1.12)	0.67*	(0.47, 0.95)	0.87	(0.65, 1.17)	0.75	(0.54, 1.05)
Ever Smoking Status	0.99	(0.74, 1.31)	0.99	(0.72, 1.36)	1.03	(0.78, 1.35)	0.99	(0.73, 1.34)

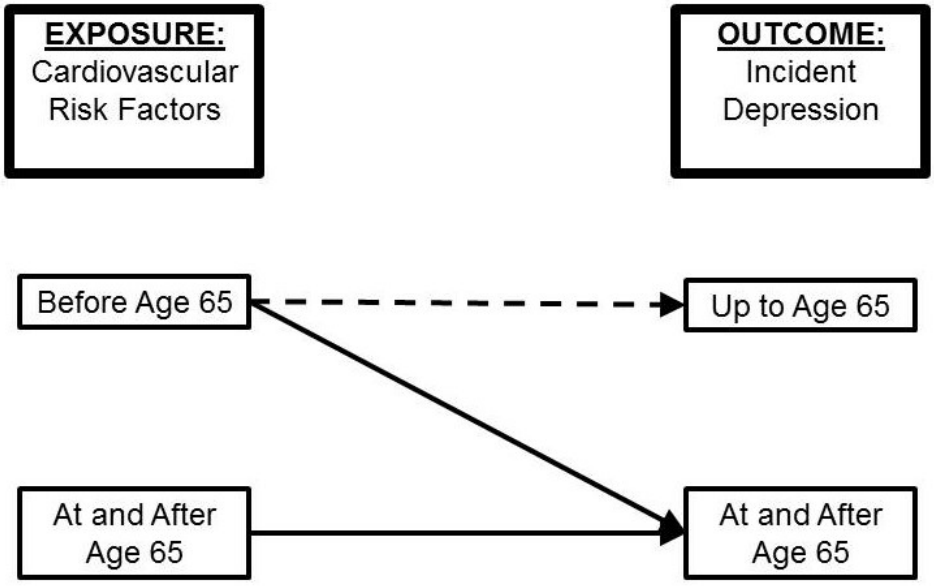
*P<0.05 **Overweight or obese defined as 25kg/m^2 or greater. [+] Adjusted by race, baseline age, enrollment wave, physical activity at age 70 or age 75, and heavy alcohol use at age 70 or age 75. FCRS = Framingham Cardiovascular Disease Risk Score

Table 9. Differences in the associations of vascular burden and cardiovascular risk factors with incident clinical depression before and after ages 70 and 75 among men who survived depression-free to age 70 (N=733) or 75 (N=521). Data from the Johns Hopkins Precursors Study (1947-2011).

	Before Age 70		Age 70 and Older		Before Age 75		Age 75 and Older	
	Hazard Ratio	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**	**Hazard Ratio**	**95% Confidence Interval**
Vascular Burden (FCRS score)	3.81*	(1.13, 12.87)	1.17	(0.46, 3.02)	---	---	---	---
Diabetes	2.52	(0.97, 6.54)	2.59	(0.97, 6.89)	1.98	(0.68, 5.78)	1.57	(0.36, 6.82)
Hypertension	2.15*	(1.11, 4.15)	1.29	(0.46, 3.67)	3.63*	(1.45, 9.10)	1.02	(0.20, 5.18)
Hyperlipidemia	2.19*	(1.10, 4.35)	2.74*	(1.12, 6.71)	2.20	(0.97, 4.98)	1.44	(0.39, 5.25)
Overweight or Obese Status	1.28	(0.67, 2.43)	1.05	(0.14, 8.06)	1.25	(0.58, 2.68)	---	---
Ever Smoking Status	1.78	(0.52, 6.08)	1.26	(0.65, 2.42)	0.83	(0.10, 6.62)	1.14	(0.53, 2.45)

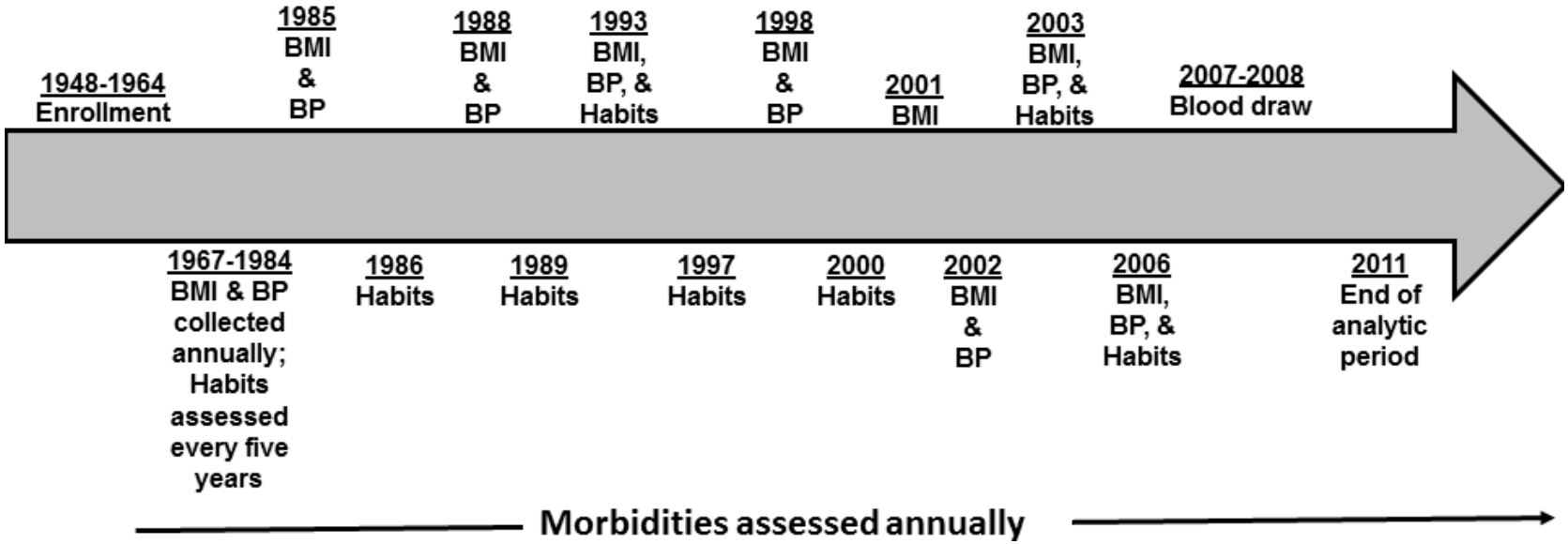
*P<0.05 **Overweight or obese defined as 25kg/m^2 or greater. $^{+}$Adjusted by race, baseline age, enrollment wave, physical activity at age 70 or age 75, and heavy alcohol use at age 70 or age 75. FCRS = Framingham Cardiovascular Disease Risk Score

Figure 1. Conceptual framework for the analysis



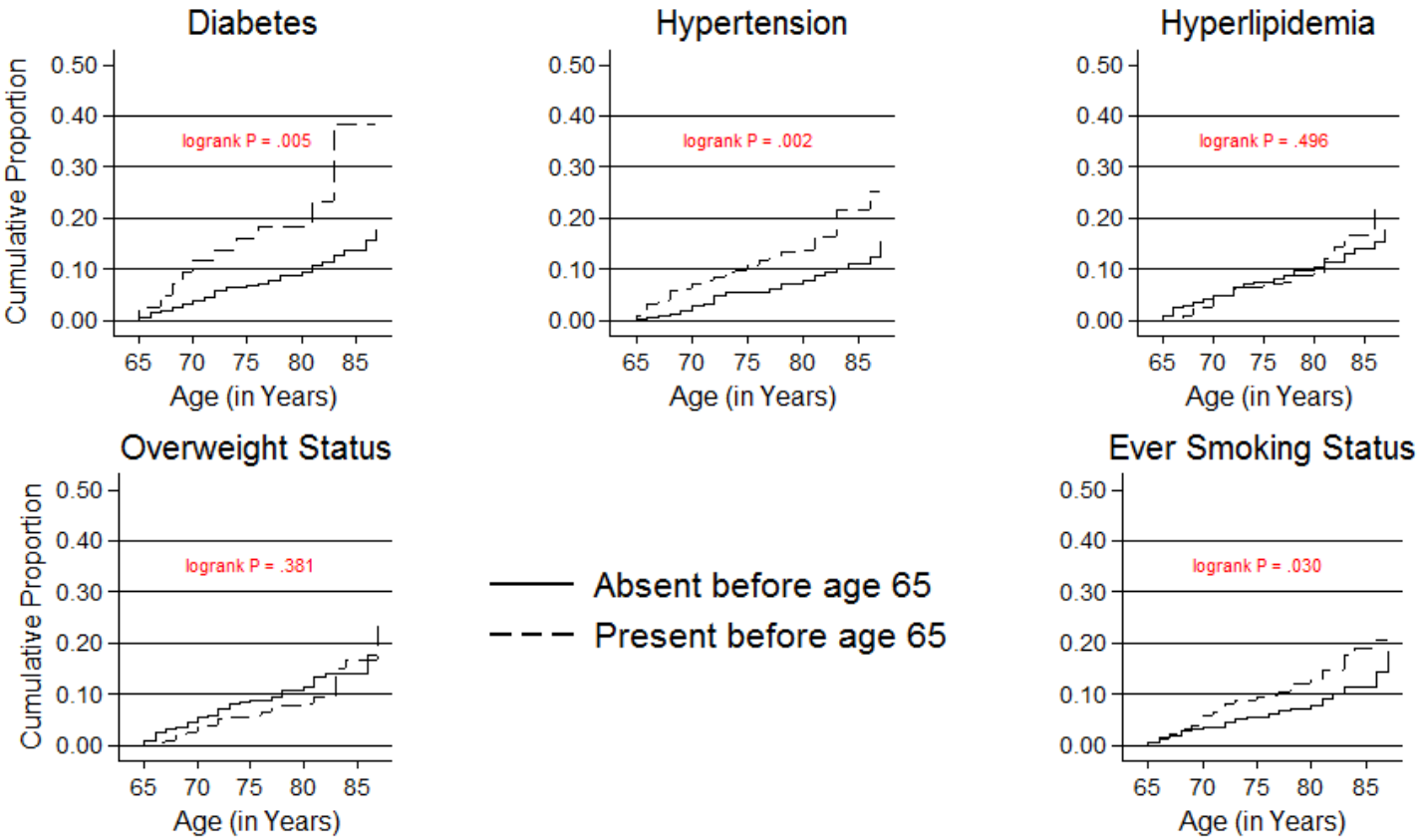
The dotted line illustrates the association of cardiovascular risk factors occurring before age 65 and the onset of incident depression up to age 65, using the full cohort. The solid lines show the association between cardiovascular risk factors occurring before age 65 or at and after age 65 and the onset of incident depression at and after age 65, using a subset of the cohort who survived up to age 65. Cardiovascular risk factors occurring after the onset of incident depression were excluded from the analysis. We used the cutoff of age 65 since onset after age 65 years was one of the cardinal features of vascular depression.

Figure 2. Brief timeline of data collection in the Johns Hopkins Precursors Study



Diagnoses for morbidities, cardiovascular disease, hypertension, and depression, were assessed approximately annually after graduation from medical school. Data about health behaviors (body mass index (BMI), blood pressure (BP) measurements) and habits (smoking status and frequency of alcohol consumption) were assessed at enrollment into the study around medical school graduation. These characteristics were assessed every five years from 1966-1984. After 1984, BMI and BP measurements were assessed in 1985, 1988, 1993, 1998, 2001 (BMI only), 2002, 2003, and 2006. Hypertension was defined as self-reported blood pressure ≥160/95 mm Hg on one annual questionnaire, ≥140/90 mm Hg on ≥2 annual questionnaires, or as hypertension requiring drug therapy (Klag et al., 2002; Wang et al., 2008). Participants self-reported multiple blood pressure readings varying from one to seven per questionnaire on approximately annual questionnaires, so an average of the SBPs was taken for each age of reported blood pressures. After 1984, habits were assessed in 1986, 1989, 1993, 1997, 2000, 2003, and 2006. Blood draw measures consisted of a complete blood panel with measures on total and HDL cholesterol. Total cholesterol was collected during medical school and in 2007-2008. HDL cholesterol was only collected in 2007-2008.

Figure 3. Kaplan-Meier plots of risk of incident clinical depression after age 65 by the presence of cardiovascular risk factors before age 65 (N=821).



The x-axis is age in years, and y-axis is the depression-free survival probability. These plots use data from participants who were depression-free before age 65.

Persistent Depressive Symptoms as Partial Mediators in the Associations between Subclinical Cardiovascular Disease with Onset of Mild Cognitive Impairment and Dementia

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Abstract

***Introduction*:** Depression may underlie the association between cardiovascular disease and dementia, yet the causal mechanism is unclear.

***Methods*:** Causal mediation methodology was implemented to examine whether persistent depressive symptoms, defined as two consecutive scores ≥8 on the 10-item Center for Epidemiologic Studies-Depression Scale, partially mediated the association of baseline subclinical cardiovascular disease (CVD) with MCI/dementia onset in an analytic sample from the Cardiovascular Health Study (N=2,450). Excluded were those with baseline clinical CVD, MCI/dementia occurring before 5 years from baseline, and missing persistent depressive symptoms (n=3,438). Total effect was decomposed into direct and indirect effects (via persistent depressive symptoms), obtained from accelerated failure time model with weights derived from multivariable logistic regression of persistent depressive symptoms on subclinical CVD. Analyses were adjusted by age, race, sex, poverty status, marital status, and depressive symptoms at baseline.

***Results*:** Participants contributed 20,994 person-years of follow-up with a median follow-up time of 9.4 years. Time to MCI/dementia is lower by a factor of 0.88 among those with subclinical CVD than those without subclinical CVD (95% Confidence Interval, [CI]: 0.83, 0.93). The total effect of subclinical CVD on MCI/dementia onset was decomposed into a direct effect (Time Ratio, [TR]=0.95, 95% CI: 0.92, 0.98) and indirect effect (TR=0.92, 95% CI: 0.88, 0.97). 64.5% of total effect was mediated via persistent depressive symptoms.

***Conclusions*:** Persistent depressive symptoms partially mediate the association of subclinical CVD with MCI/dementia onset. Depression screenings among older adults with detectable vascular damage could be beneficial in reducing the risk of MCI/dementia.

Key Terms: depressive symptoms, subclinical cardiovascular disease, mild cognitive impairment, dementia

Introduction

Cerebrovascular changes and depression are risk factors of cognitive decline and all-cause dementia (Alexopoulos et al., 2001; Jorm, 2010). Older adults with cardiovascular disease, such as coronary heart disease, may also have late-life depressive symptoms (Steffens, Krishnan, Crump, & Burke, 2002; Thomas, Kalaria, & O'Brien, 2004). About 22% of community-dwelling older adults with depressive symptoms had coronary heart disease (Steffens et al., 2002). Those with late-life depressive symptoms have a two-fold increase in the risk of developing mild cognitive impairment (MCI) and dementia, compared to those without late-life depressive symptoms (Jorm, 2010; Snowden et al., 2015). Mood disorders may underlie the association between clinical CVD and cognitive decline (Alexopoulos et al., 1997), suggesting that mood disorders may partially mediate the association between CVD and cognitive decline.

Although clinical CVD and late-onset depression are associated with one another, the relative ordering of clinical CVD and late-onset depression is unclear. Studies have shown a longitudinal association between clinical CVD and onset of depression (Sheline et al., 2006) as well as depression and the onset of clinical CVD (Ariyo et al., 2000). Subclinical CVD is a strong predictor of future clinical CVD (Kuller et al., 2006), so subclinical CVD could be a surrogate for some vascular damage sustained to the vascular pathway. Once there is vascular damage, this may lead to the development of late-onset depression, resulting in a cascade towards dementia (Taylor, Aizenstein, & Alexopoulos, 2013).

In this study, we sought to elucidate how depressive symptoms may affect the association between subclinical CVD and the known neurodegenerative process with the

combination of MCI and dementia. To do this, we used the counterfactual approach to causal mediation using time-to-event data (Lange & Hansen, 2011). We examined the mediating role of persistent depressive symptoms on the association between subclinical CVD with MCI/dementia among those without clinical CVD. We hypothesized that persistent depressive symptoms partially mediate the association of subclinical CVD with MCI/dementia onset.

Methods

Study Participants

There were 5,888 participants from the Cardiovascular Health Study (CHS), of which 3,602 participants agreed to undergo at least one brain magnetic resonance imaging (MRI) during the study. The CHS is a prospective cohort study of risk factors for coronary heart disease and stroke in adults 65 years and older. Participants are from four field centers located in Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh (Allegheny County), Pennsylvania. The CHS design and recruitment strategy is described in more detail elsewhere (Fried et al., 1991; Lopez, Jagust, DeKosky, & et al., 2003; Lopez, Jagust, Dulberg, & et al., 2003). We excluded those with baseline clinical CVD (N=783), prevalent dementia (N=145), those with MCI/dementia within five years of baseline (N=138), and those missing persistent depressive symptoms (N=86), resulting in 2,450 participants.

Subclinical Cardiovascular Disease

The baseline examination included a detailed medical history, list of current medications, blood, blood pressure, electrocardiogram, ultrasonography of carotid arteries, and an echocardiogram in 1989-1990 (Chaves et al., 2004; Kuller et al., 2006). Subclinical cardiovascular disease was defined as having at least one of the following: (1) an ankle-arm-systolic blood pressure ratio≤0.9, (2) a percentage of stenosis of the internal

carotid artery (based on ultrasonographic findings) of more than 25%, (3) intimal medial thickness of the internal or common carotid artery higher than the 80th percentile of the CHS distribution, or (4) positive findings for angina or claudication on the Rose questionnaire without clinical history of angina or claudication (Chaves et al., 2004; Kuller et al., 2006). Methods for the development of the composite index of subclinical cardiovascular disease are described elsewhere (Kuller et al., 1994).

Persistent Depressive Symptoms

The 10-item Center for Epidemiologic Studies-Depression (mCES-D), a self-reported measure of depressive symptoms experienced in the past week, was used to quantify clinically relevant depressive symptoms approximately annually (Andresen, Malmgren, Carter, & Patrick, 1994). Its 10 items are coded on a scale of 0 to 3 points, for a maximum of 30 points, and focus on mood (5 items), level of irritability (1 item), energy level (2 items), concentration (1 item), and sleep (1 item). Higher score indicates greater depressive symptoms (Andresen et al., 1994). The reliability of the mCES-D (Cronbach α statistic, 0.80) is slightly lower than the original 20-item CES-D (Cronbach α statistic, 0.86), and there is a 0.88 correlation between the 10-item and 20-item versions of the CES-D (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993). Persistent depressive symptoms were defined as having two consecutive mCES-D scores of 8 or more on the 10-item mCES-D 2-3 years after baseline (Carnetheon et al., 2007).

Classification of Mild Cognitive Impairment and Dementia

The classification of MCI and dementia was performed in two stages (Lopez, Jagust, DeKosky, et al., 2003). During the first stage, the sample was stratified into high and low risk of possible dementia among the living and dead participants, based on evaluation of cognitive testing, changes in cognitive scores, nursing home admission, vital status, and history of stroke. Among living participants, high risk of possible dementia was defined if participants had one of the following: 3MS score at one of the two most recent clinical visits, a 5-point decline in 3MS from MRI to last contact, a TICS score <28 and Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) score>3.6, history of incident stroke, history of dementia, or current residence in a nursing home. Medical records were not limited to hospitalizations (Lopez et al., 2003). Among dead participants, participants were classified at high risk of dementia if they had at least one of the following: 3MS<80 within two years of death, 5-point decrease in 3MS from MRI to year closest to death, and TICS score<28, IQCODE score>3.6 within two years of death, diagnosis of dementia, or history of incident stroke, or non-white. High-risk whites and all African Americans (due to small sample size) were subjected to detailed evaluation of dementia diagnosis in three out of the four clinics (Lopez, Jagust, DeKosky, et al., 2003). All participants were evaluated at the fourth clinic located in Pittsburgh.

Those classified as MCI and dementia cases were then reviewed by a dementia adjudication committee, which used standardized criteria for MCI and dementia diagnosis (Lopez, Jagust, DeKosky, et al., 2003). MCI and dementia were combined as an outcome, since both represent the same disease pathway leading to all-cause dementia and MCI predicts conversion to dementia (Bruscoli & Lovestone, 2004).

Adjustment Covariates

Baseline covariates included age, race, male sex, poverty status, marital status, education level, ApoE ε4 status and depressive symptoms. Race was defined as either Caucasian vs. non-white. Poverty status was defined using the income cut-off of $11,770 per Federal Poverty Level Guidelines (Dickon, 2015). Marital status was defined as either being married vs. unmarried. Education level was defined as either being a high school graduate or not. ApoE ε4 status was categorized as having at least one allele or not (Lopez, Jagust, Dulberg, et al., 2003). Depressive symptoms were baseline mCES-D continuous scores. All models were adjusted by baseline covariates.

Statistical Analysis

We evaluated differences between those with and without baseline subclinical CVD at baseline, using t-tests for continuous variables and $\chi 2$ tests for categorical variables. Also, we examined the incidence and prevalence of MCI/dementia and

persistent depressive symptoms in the sample restricted to those having at least one MRI and not having baseline clinical CVD.

We estimated Kaplan-Meier survival curves to show differences in the cumulative incidence of MCI/dementia by presence and absence of subclinical CVD (Kaplan & Meier, 1958). A log-rank test was used to test the difference of the cumulative proportions of MCI/dementia onset between presence and absence of baseline subclinical CVD (Bland & Altman, 2004). Time from the first study visit, otherwise known as baseline, was the time-scale used in the analysis. Participants contributed time from baseline until MCI/dementia onset, loss to follow-up, or administrative censoring in 1999.

Figure 1 describes the framework for causal mediation to test whether the association of subclinical CVD with MCI/dementia onset was mediated by persistent depressive symptoms. Baseline subclinical CVD was the exposure of interest. Two-year lags were introduced in each pathway between exposure and mediator as well as mediator and outcome. Persistent depressive symptoms, the mediators, were measured 2-3 years after baseline (Figure 1). A multivariable logistic regression model was used to examine the association between exposure-mediator relationship. The outcome, time to MCI/dementia onset, was measured five years after baseline (Figure 1). We used a parametric accelerated failure time model (AFTM) using a Weibull distribution to determine the association between subclinical CVD and time to MCI/dementia onset, since the proportionality hazard assumption was not met. AFTMs are an alternative to Cox proportional hazards models when the proportionality hazard assumption is not met (Patel, Kay, & Rowell, 2006).

Mediation analysis was performed using the approach proposed by Lange & Hansen (2011) and VanderWeele (2011). Let A be baseline subclinical cardiovascular disease, T time to MCI/dementia onset, M persistent depressive symptoms, and C a set of baseline covariates (Lange & Hansen, 2011; Rochon, du Bois, & Lange, 2014). Let T_a be the counterfactual event time if A had taken value a, T_{am} the counterfactual event time if A had taken value a and M had taken value m, and T_{aMa^*} be the event time when the exposure is set to a, but the mediator is set to the value it would have had if the exposure had been set to a^*. The total effect can be decomposed into natural direct and indirect effects in the following way: $\lambda_{Ta}(t) - \lambda_{Ta^*}(t) = [\lambda_{TaMa}(t) - \lambda_{TaMa^*}(t)] + [\lambda_{TaMa^*}(t) - \lambda_{Ta^*Ma^*}(t)]$ (Grotta, 2012). Model assumptions include that (1) no unmeasured confounding of the exposure-outcome relationship, (2) no unmeasured confounding of the exposure-mediator relationship, (3) no unmeasured confounding of the mediator-outcome relationship, and (4) no unmeasured confounding of the mediator-outcome relationship after prior exposure (Lange & Hansen, 2011; Rochon et al., 2014).

We estimated direct and indirect effects by modeling weighted AFTM with a Weibull distribution, using a duplicated dataset with two replications of the values of the exposure. This approach is similar to one used by Rochon et al. (2014) with the exception that we used AFTM, not a Cox Proportional Hazards model. In the first replication, A^* was set to the original value of baseline subclinical CVD, whereas, in the second replication, A^* was set to the opposite or "counterfactual" value of the subclinical CVD. Weights were determined by $W^c = P(M|A^*, C)/P(M|A, C)$. The proportions for the weights were estimated from a multivariable logistic regression model of persistent depressive symptoms on subclinical CVD and baseline covariates (Lange & Hansen,

2011; Rochon et al., 2014). Standard errors and 95% confidence intervals were determined by 5,000 bootstrap simulations. The weighted AFT model analysis was performed in R version 3.1.2 (*R: A Language and Environment for Statistical Computing*, 2013). All other analyses were done in Stata 13.1 (StataCorp, 2013).

Sensitivity Analyses

We conducted two sensitivity analyses. First, to test if we adequately adjusted by baseline covariates, we use propensity score matching, since the distribution of exposed and unexposed groups was unequal (Ridgeway, McCaffrey, Morral, Burgette, & Griffin, 2014). We assessed the adequacy of matching by performing a series of diagnostic checks (Ho, Imai, King, & Stuart, 2007; Ridgeway et al., 2014). Propensity scores were assigned to each participant, based on estimates from a multivariable logistic regression using demographic characteristics, (i.e., age, sex, race, poverty status, marital status, education level), ApoE ε4 status, and baseline depressive symptoms. We conducted the main statistical analysis using the matched dataset. The analysis was further adjusted by baseline covariates to account for small differences in the matched sample (Ho et al., 2007).

Second, we examined incident dementia as a separate outcome and conducted the same analysis to determine whether inferences differed. Persistent depressive symptoms may account for more of the total effect of subclinical CVD on incident dementia.

Results

Sample Characteristics

Table 1 shows the sample characteristics for each model for the mediating effect of persistent depressive symptoms on the association between subclinical CVD and MCI/dementia onset. Those with baseline subclinical CVD were likely to be older, male, current smokers, and impoverished as well as have diabetes, treated hypertension, higher systolic blood pressure, lower HDL cholesterol, and shorter time on study, as compared to those without baseline subclinical CVD (all p's<0.05) (Table 1). Also, those with baseline subclinical CVD were less likely to be high school graduates than those without baseline subclinical CVD (p<0.01) (Table 1). Those with and without baseline subclinical CVD were similar in terms of race, ethnicity, marital status, baseline depressive symptoms, ApoE ε4 status, antidepressant mediations, body mass index, and total cholesterol (all p's>0.05) (Table 1).

Table 2 shows the frequencies and percentages of the overall sample restricted to those without baseline clinical CVD. There were 1,677 (65.4%) participants who developed neither persistent depressive symptoms nor MCI/dementia, 159 (6.2%) who developed persistent depressive symptoms only, 592 (23.1%) who developed MCI/dementia only, and 137 (3.4%) who developed both persistent depressive symptoms (Table 2). Of those who developed both persistent depressive symptoms and MCI/dementia, 136 (99.3%) had persistent depressive symptoms prior to year 5 and 1 (0.7%) had MCI/dementia onset before persistent depressive symptoms (Table 2).

Figure 2 shows Kaplan-Meier survival curves comparing the risk of MCI/Dementia between those with and without baseline subclinical CVD. The cumulative proportion of MCI/dementia is higher among those with baseline subclinical CVD than those without baseline subclinical CVD ($p<0.01$). Participants contributed 20,994.88 person-years to the study with mean follow-up time of 8.78 years (median=9.37 years).

Mediating Effect of Persistent Depressive Symptoms on the Association of Subclinical CVD with MCI/Dementia Onset

The total effect of subclinical CVD on MCI/dementia onset and its decomposition into natural indirect and direct effects is shown in Table 3. The time ratio (TR) for total effect for the association between subclinical CVD and MCI/dementia onset was 0.88 (95% Confidence Interval, [CI]: 0.83, 0.93). The time to MCI/dementia onset for those with baseline subclinical CVD is decreased by a factor of 0.83, as compared to those without baseline subclinical CVD (Table 3). The total effect was decomposed into a direct effect of subclinical CVD (TR=0.95, 95% CI: 0.92, 0.98) and indirect effect of persistent depressive symptoms (TR=0.92, 95% CI: 0.88, 0.97) (Table 3). The proportion mediated through persistent depressive symptoms was 64.5% on the log TR scale.

Sensitivity Analyses

Results were similar when we used a matched sample based on propensity scores (Table 4). Figures 4 and 5 show diagnostic plots for propensity score matching. The time ratio for the total effect of subclinical CVD on MCI/dementia onset was 0.88 (95% CI: 0.83, 0.93). Among those with similar baseline characteristics, the time to MCI/dementia onset for those with subclinical CVD decreased by a factor of 0.88, as compared to those without baseline subclinical CVD. The total effect was decomposed into the direct effect (TR=0.95, 95% CI: 0.83, 0.93) and the indirect effect (TR=0.92, 95% CI: 0.88, 0.97) (Table 4).

Additionally, we examined the indirect effect of persistent depressive symptoms on the association between subclinical CVD and onset of incident dementia. First, we evaluated survival curves from Kaplan-Meier plots to assess the association between subclinical CVD and incident dementia (Figure 3). The cumulative proportion of incident dementia is higher among those with baseline subclinical CVD than those without baseline subclinical CVD ($p<0.01$).

Table 5 shows the decomposition of the total effect of subclinical CVD and incident dementia into the direct and indirect effects. The time ratio for the total effect of subclinical CVD on onset of incident dementia was 0.86 (95% CI: 0.73, 1.04) (Table 5). The time to onset of incident dementia for those with baseline subclinical CVD decreased by a factor of 0.86, as compared to those without baseline subclinical CVD. However, this estimate was not statistically significant. The total effect was decomposed into the direct effect (TR=0.87, 95% CI: 0.79, 0.96) and the indirect effect (TR=0.99, 95% CI: 0.86, 1.16). Only the direct effect was significant (Table 5). Persistent depressive symptoms mediated 6.66% of the association between subclinical cardiovascular disease

and onset of incident dementia. Results were similar when we used a matched sample based on propensity score matching.

Discussion

Persistent depressive symptoms partially mediated the association of subclinical CVD with MCI/dementia onset even after propensity score adjustment. Persistent depressive symptoms accounted for over half of the total association between subclinical CVD and MCI/dementia onset. These findings suggest that mood disorders may underlie the association between subclinical CVD and MCI/dementia onset.

These findings are consistent with Jorm (2010) and Taylor et al. (2013) who noted that existing vascular disease could increase the risk of depression and vascular dementia. There are several mechanisms that could potentially explain the association among subclinical CVD, persistent depressive symptoms, and MCI/dementia onset (Taylor et al., 2013). One potential mechanism is the occurrence of depression in older adults via hypometabolism of dorsal cortical regions and hypermetabolism of the ventral limbic structures (Alexopoulos, 2005). Neurobiological changes resulting from age, comorbidities, and stress may compromise frontolimbic structures. As severity of the neurobiological changes worsens, mood circuit functions are affected, thus potentially leading to depression and subsequent dementia (Alexopoulos, 2005). Another potential pathway underlying the association among CVD, depression, and MCI/dementia is that focal damage from white matter hyperintensities, common in people with cardiovascular risk factors and cardiovascular disease, can lead to deficits in neural circuitry (Alexopoulos, 2002).

Another potential mechanism of the association among subclinical CVD, persistent depressive symptoms, and MCI/dementia is the inflammatory hypothesis (Taylor et al., 2013). Older adults may have proinflammatory states resulting from aging

and disease processes. Immune dysregulation may increase depression onset (Harrison et al., 2009) and contribute neurodegenerative process (Koyama et al., 2012; Rubio-Perez & Morillas-Ruiz, 2012).

Our study has several strengths. First, there was a large sample size of older adults with heterogeneity in demographic characteristics with up to 10 years of follow-up. Second, the CHS has a detailed evaluation of subclinical CVD and MCI/dementia. Third, the relative ordering of subclinical CVD, persistent depressive symptoms, and MCI/dementia onset was temporally intact for the mediation analysis, since persistent depressive symptoms occurred before MCI/dementia onset among those who had both persistent depressive symptoms and MCI/dementia. Also, there was minimal (3%) missingness for persistent depressive symptoms. All participants had measures on subclinical CVD and MCI/dementia onset.

There are several limitations. First, a main assumption of the mediation analysis is that all relevant confounders are included in the analysis. We included all potential baseline confounders, such as baseline demographic characteristics, baseline depressive symptoms, and ApoE ε4 status. Moreover, when we used AFTM with the matched dataset based on propensity scores, we obtained similar results. Another limitation is the requirement of no other variables that confound the mediator-outcome association, but this is untestable in observational studies (Lange & Hansen, 2011). Besides these limitations, there was no indirect effect of persistent depressive symptoms on the association between subclinical CVD and onset of incident dementia. Incident dementia represents a more severe neurodegenerative process. Also, there could have been a limited number of cases to find an indirect effect.

Persistent depressive symptoms may underlie the association between vascular processes and MCI/dementia onset. Older adults who have experienced a cardiovascular event are prone to subsequent depression and dementia. Screening for depressive symptoms prior to a diagnosis of clinical CVD may delay or reduce the incident MCI/dementia cases in older adults, especially among older adults with some evidence of vascular damage. A future direction of this study is to examine the indirect effects of the different domains of the mCES-D, i.e., somatic complaints, interpersonal conflicts, depressed affect, and positive affect, on the association of early vascular damage and cognitive decline. We may further elucidate what domain of depression may affect the disease process leading to dementia.

References

Alexopoulos, G.S. (2002). Frontostriatal and limbic dysfunction in late-life depression. *The American Journal of Geriatric Psychiatry*, 10(6), 687-695.

Alexopoulos, G.S. (2005). Depression in the elderly. *Lancet*, 365, 1961-1970.

Alexopoulos, G.S., Kiosses, D.N., Heo, M., Murphy, C.F., Shanmugham, B., & Gunning-Dixon, F. (2001). Executive dysfunction and the course of geriatric depression. *Biological Psychiatry*, 58, 204-210.

Alexopoulos, G.S., Meyers, B.S., Young, R.C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular Depression' Hypothesis. *Archives of General Psychiatry*, 54, 915-922.

Andresen, E.M., Malmgren, J.A., Carter, W.B., & Patrick, D.L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventive Medicine*, 10(2), 77-84.

Ariyo, A.A., Haan, M., Tangen, C.M., Rutledge, J.C., Cushman, M., Dobs, A., . . . Cardiovascular Health Study Collaborative Research Group. (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. *Circulation*, 102, 1773-1779.

Bland, J.M., & Altman, D.G. (2004). The logrank test. *BMJ : British Medical Journal*, 328(7447), 1073-1073.

Bruscoli, M. & Lovestone, S. (2004). Is MCI really just early dementia? A systematic review of conversion studies. *International Psychogeriatrics*, 16(2), 129-140.

Carnetheon, M.R., Biggs, M.L., Barzilay, J.I., Smith, N.L., Vaccarino, V., Bertoni, A.G.,

. . . Siscovick, D. (2007). Longitudinal association between depressive symptoms and incident Type 2 diabetes mellitus in older adults: The Cardiovascular Health Study. *Archives of Internal Medicine*, 167, 802-807.

Chaves, P.H., Kuller, L.H., O'Leary, D.H., Manolio, T.A., Newman, A.B., & Cardiovascular Health Study. (2004). Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *American Journal of Geriatric Cardiology*, 13(3), 137-151.

Dickon, R.E. (2015). *Annual Update of the HHS Poverty Guidelines*. Washington, D.C.: Federal Register.

Fried, L.P., Borhani, N.O., Enright, P., Furberg, C.D., Gardin, J.M., Kronmal, R.A., . . . Weiler, P.G. (1991). The Cardiovascular Health Study: design and rationale. *Annals of Epidemiology*, 1(3), 263-276.

Grotta, Alessandra. (2012). *Causal Mediation Analysis on Survival Data: An Application on the National March Cohort*. Milan, Italy: Universita degli Studi di Milano - Bicocca.

Harrison, N.A., Brydon, L., Walker, C., Gray, Marcus A., Steptoe, A., & Critchley, H.D. (2009). Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biological Psychiatry*, 66(5), 407-414.

Ho, D., Imai, K., King, G., & Stuart, E. (2007). Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis*, 15, 199-236.

Jorm, A.F. (2010). Is depression a risk factor for dementia or cognitive decline?

Gerontology, 46, 219-227.

Kaplan, E.L., & Meier, P. (1958). Non-parametric estimation from incomplete observations. *Journal of American Statistical Association*, 53, 457-481.

Kohout, F.J., Berkman, L.F., Evans, Denis A., & Cornoni-Huntley, Joan. (1993). Two Shorter Forms of the CES-D Depression Symptoms Index. *Journal of Aging and Health*, 5(2), 179-193.

Koyama, A., O'Brien, J., Weuve, J., Blacker, D., Metti, A.L., & Yaffe, K. (2012). The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 68(4), 433-440.

Kuller, L.H., Arnold, A.M., Psaty, B.M., Robbins, J.A., O'Leary, D.H., Tracy, R.P., . . . Chaves, P.H. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the cardiovascular health study. *Archives of Internal Medicine*, 166(1), 71-78.

Lange, T. & Hansen, J.V. (2011). Direct and indirect effects in a survival context. *Epidemiology*, 22(4), 575-581.

Lopez, O. L., Jagust, W. J., DeKosky, S. T., Becker, J.T., Fitzpatrick, A., Dulberg, C., …, Kuller, L.H. (2003). Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 1. *Archives of Neurology*, 60(10), 1385-1389.

Lopez, O. L., Jagust, W. J., Dulberg, C., Becker, J.T., DeKosky, S.T., Fitzpatrick, A., …, Kuller, L.H. (2003). Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: Part 2. *Archives of Neurology*,

60(10), 1394-1399.

Patel, K., Kay, R., & Rowell, L. (2006). Comparing proportional hazards and accelerated failure time models: an application in influenza. *Pharmaceutical Statistics*, 5(3), 213-224.

R: A Language and Environment for Statistical Computing. (2013). Vienna, Austria: R Foundation for Statistical Computing.

Ridgeway, G., McCaffrey, D., Morral, A., Burgette, L., & Griffin, B.A. (2014). *Toolkit for Weighting and Analysis of Nonequivalent Groups: A Tutorial for the R TWANG Package*. Santa Monica, CA: RAND Corporation.

Rochon, J., du Bois, A., & Lange, T. (2014). Mediation analysis of the relationship between institutional research activity and patient survival. *BMC Medical Research Methodology*, 14(1), 1-8.

Rubio-Perez, J.M. & Morillas-Ruiz, J.M. (2012). A review: inflammatory process in Alzheimer's disease, role of cytokines. *The Scientific World Journal*, 2012.

Sheline, Y.I., Barch, D.M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., . . . Doraiswamy, P. M. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, 60, 58-65.

Snowden, M.B., Atkins, D.C., Steinman, L.E., Bell, J.F., Bryant, L.L., Copeland, C., & Fitzpatrick, A.L. (2015). Longitudinal association of dementia and depression. *The American Journal of Geriatric Psychiatry*, 23(9), 897-905.

StataCorp. (2013). *Stata Statistical Software: Release 13*. College Station, TX: StataCorp

LP.

Steffens, D.C., Krishnan, K.R., Crump, C., & Burke, G.L. (2002). Cerebrovascular disease and evolution of depressive symptoms in the Cardiovascular Health Study. *Stroke*, 33, 1636-1644.

Taylor, W.D., Aizenstein, H.J., & Alexopoulos, G.S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, 18, 963-974.

Thomas, A.J., Kalaria, R.N., & O'Brien, J.T. (2004). Depression and vascular disease: What is the relationship? *Journal of Affective Disorders*, 79, 81-95.

VanderWeele, T. J. (2011). Causal mediation analysis with survival data. *Epidemiology*, 22(4), 582-585.

Table 1. Characteristics of study sample

Baseline Characteristics	No Subclinical CVD N=1,062	Subclinical CVD N=1,388	p-value for difference
Age, mean(SD)	70.5 (4.0)	72.1 (4.8)	<0.01
White, n(%)	936 (88.1)	1,220 (87.9)	0.86
Hispanic, n(%)	9 (0.9)	14 (1.0)	0.27
Male, n(%)	345 (32.5)	575 (41.4)	<0.01
High School Graduate, n(%)	867 (81.6)	1,050 (75.7)	<0.01
Married, n(%)	745 (70.2)	947 (68.2)	0.31
mCES-D Score, mean (SD)	3.9 (3.9)	4.2 (4.1)	0.06
Poverty, n(%)	168 (15.8)	288 (20.8)	<0.01
ApoE ε4, n(%)	243 (22.9)	285 (20.5)	0.22
Diabetes, n(%)	49 (4.6)	118 (8.5)	<0.01
Current Smokers, n(%)	88 (8.3)	186 (13.4)	<0.01
Hypertension, n(%)	302 (28.4)	591 (42.6)	<0.01
Antihypertensive Medications n(%)	306 (28.8)	571 (41.1)	<0.01
Antidepressant Medications, n(%)	32 (3.0)	51 (3.7)	0.51
BMI, mean (SD)	26.2 (4.4)	26.6 (4.3)	0.06
SBP, mean (SD)	130.7 (18.7)	136.8 (21.8)	<0.01
Total cholesterol, mean (SD)	210.6 (35.6)	213.1 (39.0)	0.10
HDL cholesterol, mean (SD)	57.9 (16.4)	54.6 (15.2)	<0.01
Time on Study, mean (SD)	8.8 (1.4)	8.5 (1.6)	<0.01

SD=standard deviation, HDL=high density lipoprotein, mCES-D: modified Centers for Epidemiologic Studies: Depression Scale, SBP=systolic blood pressure, BMI=body mass index

Table 2. Prevalence and onset of MCI/dementia and persistent depressive symptoms among participants without baseline clinical cardiovascular disease: Results from Cardiovascular Health Study (N=2,819)

	N (%)
Incident MCI	440 (15.6%)
Prevalent dementia at baseline	145 (5.1%)
Not prevalent dementia at baseline	1,883 (66.8%)
Incident dementia	351 (12.5%)
Developed neither persistent depressive symptoms nor MCI/dementia	1,677 (65.4%)
Developed only persistent depressive symptoms	159 (6.2%)
Developed only MCI/dementia	592 (23.1%)
Developed MCI/dementia before year 5	138 (5.2%)
Developed incident dementia before year 5	108 (4.0%)
Developed both	137 (5.34%)
Persistent depressive symptoms first before year 5	136 (99.3%)
MCI/dementia first before year 5	1 (0.7%)
Co-occurring with MCI/dementia	0 (0.0%)
Time in years from baseline to persistent depressive symptoms, mean (SD)	2.9 (0.1)
Time in years from baseline to MCI/dementia, mean (SD)	8.1 (2.2)

Note: We excluded those without MRI's (N=2,286) and those with baseline clinical cardiovascular disease (N=783).

Table 3. Decomposition of total effect of subclinical cardiovascular disease and MCI/dementia onset into direct and indirect effects via persistent depressive symptoms using Accelerated Failure Time Models with a Weibull distribution

Effect (Subclinical CVD vs. no Subclinical CVD)	**Time Ratio**	**95% Confidence Interval**
Total Effect	**0.88**	**(0.83, 0.93)**
Direct Effect	**0.95**	**(0.92, 0.98)**
Indirect Effect (Through Persistent Depressive Symptoms)	**0.92**	**(0.88, 0.97)**
Percent Mediated on the Log TR Scale	64.48%	

Bolded means $p<0.05$

Note: Time Ratio (TR), TR<1, indicates a decrease in time without MCI/dementia and TR>1 indicates a prolonged time without MCI/dementia. Percent mediated on the log TR scale was calculated by: $[\ \ln(TR_{\text{indirect effect}})/\ln(TR_{\text{total effect}})]*100$.

Table 4. Decomposition of total effect of subclinical cardiovascular disease and MCI/dementia onset into direct and indirect effects via persistent depressive symptoms using Accelerated Failure Time Models with a Weibull distribution and propensity score matching

Effect (Subclinical CVD vs. No Subclinical CVD)	**Time Ratios**	**95% Confidence Interval**
Total Effect	**0.88**	**(0.83, 0.93)**
Direct Effect	**0.95**	**(0.92, 0.99)**
Indirect Effect (Through Persistent Depressive Symptoms)	**0.92**	**(0.88, 0.97)**
Percent Mediated on the Log TR Scale	65.23%	

Bolded values mean $p<0.05$.
Note: Time Ratio (TR), TR<1, indicates a decrease in time without MCI/dementia and TR>1 indicates a prolonged time without MCI/dementia. Percent mediated on the log TR scale was calculated by: $[\ \ln(TR_{\text{indirect effect}})/\ln(TR_{\text{total effect}})]*100$.

Table 5. Decomposition of total effect of subclinical cardiovascular disease and incident dementia into direct and indirect effects via persistent depressive symptoms using Accelerated Failure Time Models with a Weibull distribution

Effect (Subclinical CVD vs. No Subclinical CVD)	**Time Ratios**	**95% Confidence Interval**
Total Effect	0.86	(0.73, 1.04)
Direct Effect	**0.87**	**(0.79, 0.96)**
Indirect Effect (Through Persistent Depressive Symptoms)	0.99	(0.86, 1.16)
Percent Mediated on the Log TR Scale	6.66%	

Bolded values mean $p<0.05$.

Note: Time Ratio (TR), TR<1, indicates a decrease in time without incident dementia and TR>1 indicates a prolonged time without incident dementia. Percent mediated on the log TR scale was calculated by: $[\ln(TR_{\text{indirect effect}})/\ln(TR_{\text{total effect}})]*100$.

Figure 1. Hypothesized pathway linking cardiovascular disease, depression, Mild Cognitive Impairment, and dementia. This figure illustrates persistent depressive symptoms partially mediating the association between subclinical cardiovascular disease with onset of Mild Cognitive Impairment and dementia.

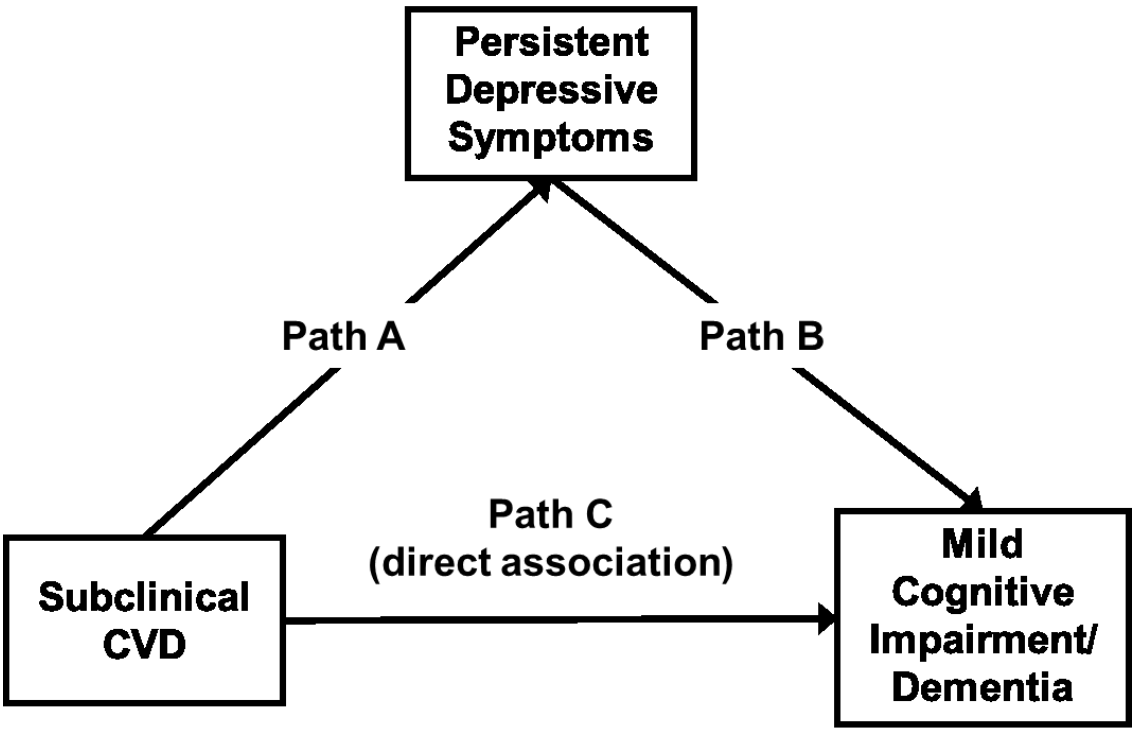
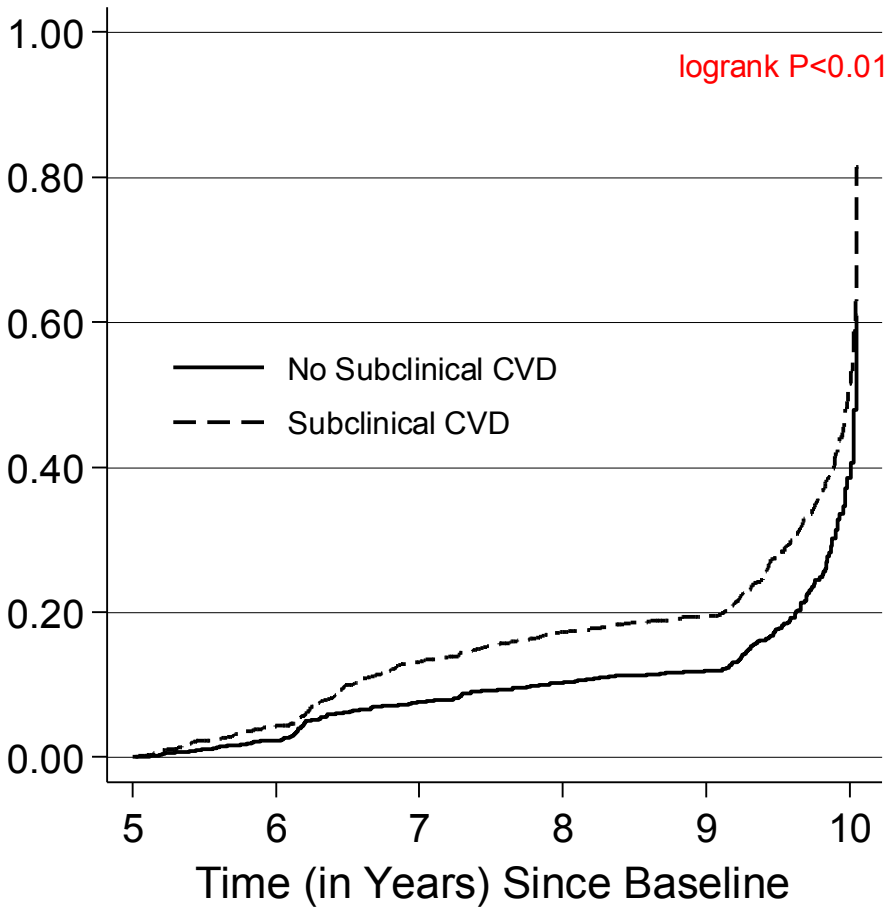
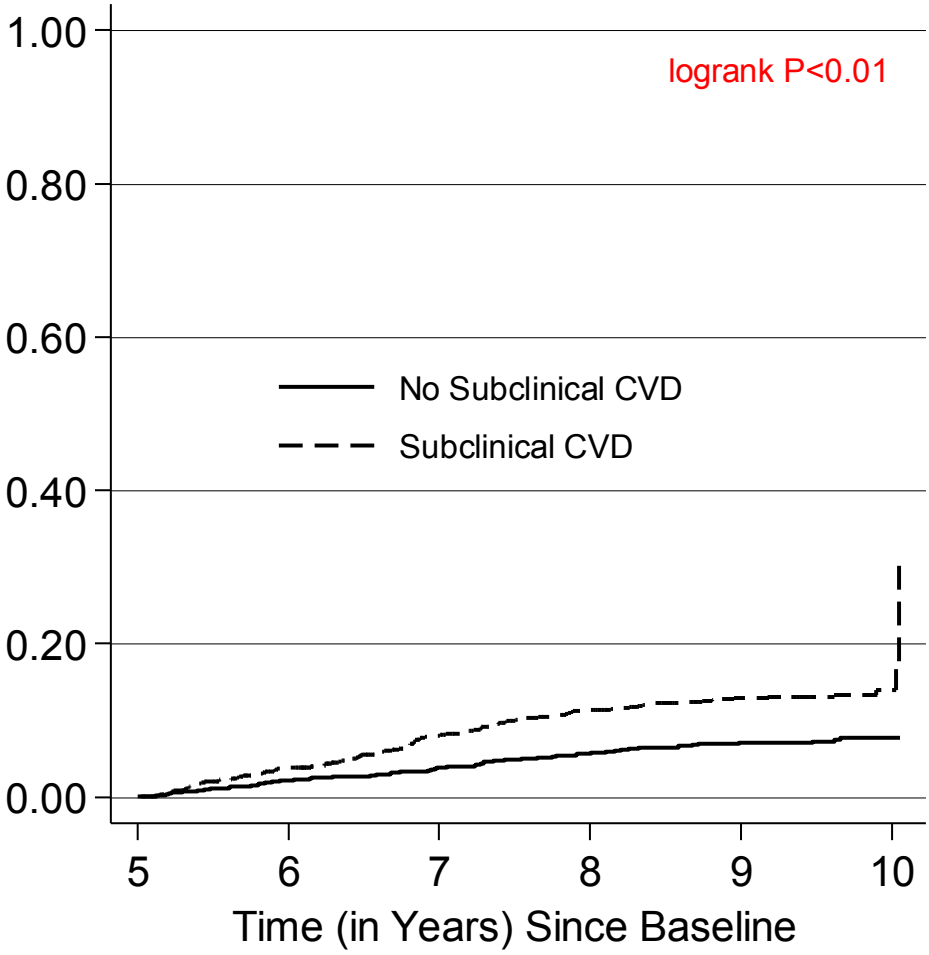


Figure 2. Kaplan-Meier plot for the association of baseline subclinical cardiovascular disease with onset of MCI/dementia five years after baseline



Number at risk						
No Subclinical CVD	1043	1006	887	844	819	34
Subclinical CVD	1348	1264	1060	982	928	33

Figure 3. Kaplan-Meier plot for the association of baseline subclinical cardiovascular disease with onset of incident dementia five years after baseline

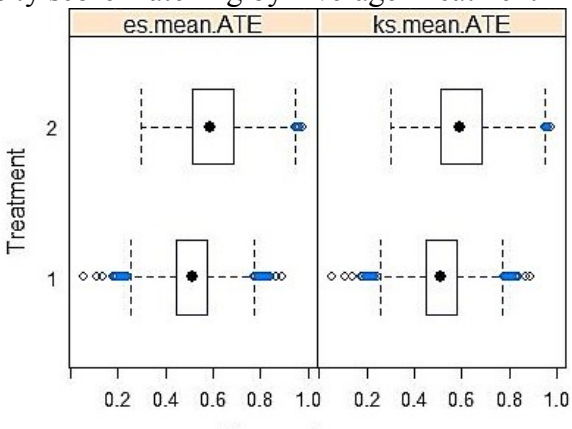


Number at risk

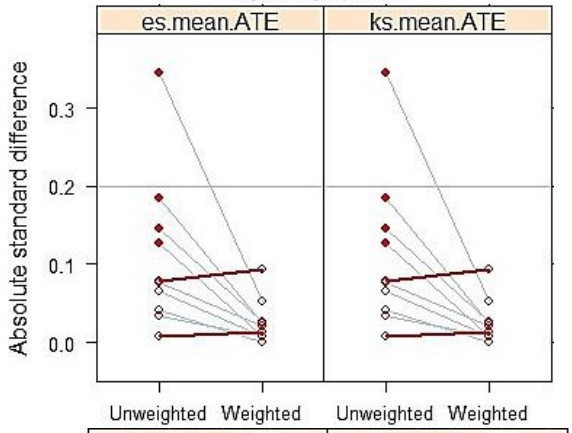
No Subclinical CVD	1043	1006	887	844	819	34
Subclinical CVD	1348	1264	1060	982	928	33

Figure 4. Diagnostic plots to compare two stopping rules (Effect Size [ES] and Kolmogorov-Smirnov [KS]) for propensity score matching by Average Treatment Effects (ATE)

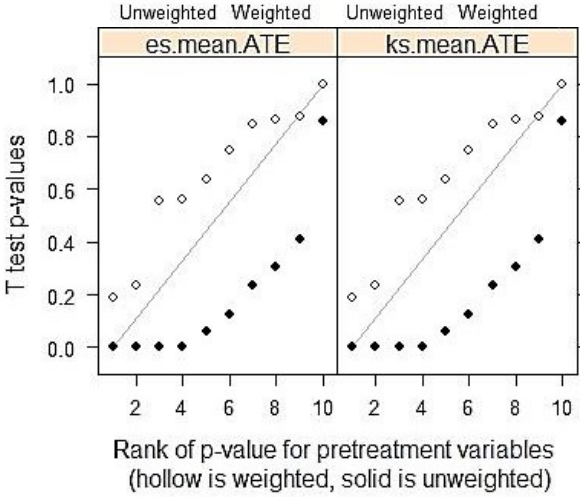
Panel A



Panel B



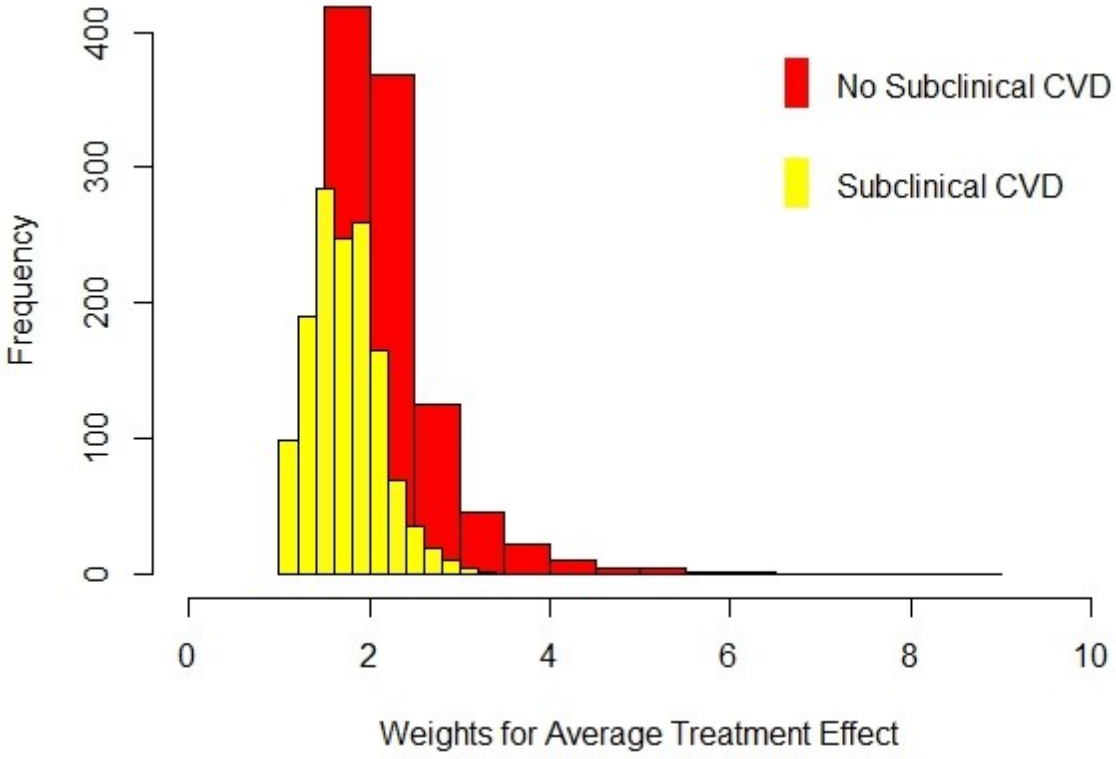
Panel C



Note: All Absolute standardized mean difference or Effect Size (es.mean.ATE) and Kolmogorov-Smirnov (ks.mean.ATE) test statistic. ES uses the effect size or the absolute standardized bias and summarizes across variables with the mean. KS uses KS statistics to assess balances and summarizes using the maximum across the variables.

Spread of the estimated propensity scores in the treatment and comparison groups for two stopping rules by boxplots (Panel A) and comparison between unweighted and weighted absolute standard differences (Panel B) and t-test p-values (Panel C):

Figure 5. Comparison of histograms of weights for average treatment effect between those with and without subclinical cardiovascular disease for propensity score matching



Subclinical Cardiovascular Disease, Persistent Depressive Symptoms, and All-Cause Mortality: An Application of Causal Mediation Approach Using Survival Data

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Abstract

Introduction: Presence of vascular damage, represented as subclinical cardiovascular disease (CVD), and depression are associated and are each independent risk factors of all-cause mortality, but the interplay between subclinical CVD and depression leading to all-cause mortality is unclear.

Methods: Using an analytic sample from the Cardiovascular Health Study (N=3,473) that excluded baseline clinical CVD, we implemented Cox Proportional Hazards model to examine the direct and indirect (via persistent depressive symptoms) effects of the association between subclinical CVD and all-cause mortality with weights derived from multivariable logistic regression model of persistent depressive symptoms on subclinical CVD. Analyses were adjusted for baseline covariates: age, race, sex, poverty status, marital status, educational level, ApoE ε4 status, and depressive symptoms. Two consecutive scores ≥8 on the 10-item Center for Epidemiologic Studies-Depression Scale defined persistent depressive symptoms.

Results: Participants contributed 55,157.1 person-years with a mean of 15.2 years of follow-up. Baseline subclinical CVD led to a higher risk of all-cause mortality (Hazard Ratio, [HR]: 1.58, 95% Confidence Interval, [CI]: 1.34, 1.87). Total effect of baseline subclinical CVD on all-cause mortality was decomposed into direct (HR=1.45, 95% CI: 1.34, 1.58) and indirect (HR=1.09, 95% CI: 0.95, 1.25) effects. 18.8% of the total effect of baseline subclinical CVD on all-cause mortality was mediated by persistent depressive symptoms.

***Conclusions**:* Subclinical CVD is a risk factor of all-cause mortality. Persistent depressive symptoms accounts for very little, if any, of the association between subclinical CVD and all-cause mortality.

Key Terms: depressive symptoms, subclinical cardiovascular disease, death

Introduction

Some of the strongest predictors of mortality are noninvasive, objective measures of both subclinical and clinical cardiovascular disease (CVD) (Fried et al., 1998). Kuller et al. (1995) developed an index of subclinical CVD, based on ankle-brachial blood pressure, carotid artery stenosis and wall thickness, positive responses of the Rose angina and claudication questionnaire from participants without clinical evidence of angina or claudication. The index of subclinical CVD was a strong predictor of developing clinical CVD and all-cause mortality after 10 or more years of follow-up (Kuller et al., 2006).

Another predictor of mortality is depressive symptoms (Ariyo et al., 2000; Barefoot & Schroll, 1996). Schulz et al. (2000) reported that milder or subthreshold forms of depression increase the risk of death in older adults. Behavioral and pathopsychological mechanisms may explain the association between depression and morality. Older, depressed adults may disengage from healthy behaviors and social situations, thus leading to neuroendocrine system dysregulation and compromise of the homeostatic immune function (Schulz et al., 2000).

CVD and depressive symptoms are associated, but these conditions may have a bi-directional relationship. Sheline et al. (2006) reported an association between clinical CVD and depression onset, whereas Ariyo et al. (2000) found that depression led to the onset of clinical CVD. The vascular depression hypothesis may help elucidate the association between CVD and depression (Alexopoulos et al., 1997). Depression may underlie the association between CVD and all-cause mortality.

One study that examined the associations among CVD, depression, and all-cause mortality was conducted by Almeida, Alfonso, Flicker, Hankey, and Norman (2012).

Using data from the Health in Men Study, Almeida et al. (2012) examined the joint effects of CVD and depression on all-cause mortality and concluded that CVD and depression did not have any synergistic effects on all-cause mortality. This study did not examine whether depression had a mediating role in the association between CVD and all-cause mortality.

The objective of this study is to determine the role in depressive symptoms in the association between subclinical cardiovascular disease and all-cause mortality. By examining an earlier part of the vascular pathway prior to the development of clinical CVD, we may find that subclinical CVD leads to elevated risk of depressive symptoms. We hypothesize that depressive symptoms partially mediate the association between subclinical CVD and all-cause mortality. To examine this objective, we will use the counterfactual approach to causal mediation using time-to-event data.

Methods

Study Sample

The study was conducted using the Cardiovascular Health Study, a community-based study of 5,888 men and women aged 65 years and older at baseline. Study design, eligibility criteria, and recruitment characteristics are available elsewhere (Fried et al., 1991). Briefly, participants underwent interview and clinical assessments annually from 1989 to 1999 and telephone follow-up visits occur to present. Hospital discharge summaries and ICD-9 codes for all hospitalizations were collected during the follow-up period (Fried et al., 1991).

We excluded those with baseline cardiovascular disease (N=1,517), those who died before Year 5 (N=456), and those with missing persistent depressive symptoms (N=442). There were 3,473 participants in this analysis.

Subclinical Cardiovascular Disease

Subclinical CVD was defined as the presence or the absence of subclinical CVD at baseline. Subclinical CVD was defined as having any one of the following at baseline: ankle-arm index less than or equal to 0.9, internal and common carotid wall thickness greater than 80th percentile, carotid stenosis greater than 25%, major ECG abnormalities, and Rose questionnaire identifying either claudication positive or angina positive without clinical history of angina or claudication (Chaves et al., 2004; Kuller et al., 2006; Kuller

et al., 1995). Methods describing the index of subclinical CVD are described elsewhere (Kuller et al., 1995).

Persistent Depressive Symptoms

Persistent depressive symptoms were defined as having two consecutive scores of 8 or more on the modified Center for Epidemiologic Studies-Depression Scale (mCES-D) (Carnetheon et al., 2007). The mCES-D is a short self-reported measure of depressive symptoms experienced during the previous week (Andresen, Malmgren, Carter, & Patrick, 1994). There are questions on mood (5 items), irritability (1 item), calories (energy) (2 items), concentration (1 item), and sleep (1 item). Items are coded on a scale from 0 (rarely or none of the time) to 3 (most or all of the time), for a maximum of 30 points. Higher score indicates greater depressive symptoms. Compared to the original 20-item CES-D, the reliability of the mCES-D (Cronbach α statistic, 0.80) is slightly lower (Cronbach α statistic, 0.86), and there is a 0.88 correlation between the 10-item CES-D and 20-item CES-D (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993).

All-Cause Mortality

There was 98% complete ascertainment of death status through 2015. Deaths were obtained through passive ascertainment of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care utilization database for hospitalizations, and through active ascertainment of contacting households

to follow up on vital status (Schulz et al., 2000). For all deaths, the cause of death was the underlying cause, not necessarily the immediate cause (Newman et al., 2009). Cause of death was adjudicated by a committee of physicians without knowledge of prior examination findings (Newman et al., 2009).

Adjustment Covariates

Additional baseline covariates included age, race, male sex, poverty status, marital status, education level, ApoE ε4, and depressive symptoms. Race was defined as Caucasian vs. non-white. Poverty status was an income cut-off below $11,770 from Federal Poverty Level Guidelines (Dickon, 2015). Marital status was coded as married vs. unmarried. Education level was defined as high school graduate vs. not. ApoE ε4 was categorized as the presence of at least one allele. Depressive symptoms were defined as baseline mCES-D scores. All models were adjusted by these baseline covariates.

Statistical Analysis

We characterized the sample at the first visit using means and percentages, and we evaluated differences among the exposures of each of the three models throughout the follow-up period, using t-tests for continuous variables and $\chi 2$ tests for categorical variables.

We estimated Kaplan-Meier survival curves to compare cumulative proportions of all-cause mortality between those with and without subclinical CVD (Kaplan & Meier,

1958). The difference in the cumulative proportions of all-cause mortality between presence and absence of baseline subclinical CVD was tested using a log-rank test (Bland & Altman, 2004). Time from the first study visit (baseline) was the time-scale used in the analysis. Participants contributed time from baseline until death, loss to follow-up, or administrative censoring in 2015.

Figure 1 shows the hypothesized direct and indirect pathways connecting baseline subclinical CVD to all-cause mortality via persistent depressive symptoms. Subclinical CVD was measured at baseline. Persistent depressive symptoms, the mediators, were measured 2-3 years after baseline, and the outcome, all-cause mortality, was ascertained at least five years from baseline up to 24 years from baseline. There were two-year lags between the exposure and the mediators as well as the mediators and the outcome.

To decompose the total effect between baseline subclinical CVD and all-cause mortality into direct and indirect effects, we used the counterfactual approach for causal mediation, as proposed by Lange and Hansen (2011) and VanderWeele (2011). The observed variables are exposure A, mediator M, outcome Y, and baseline covariates C. The counterfactual variables are $Y_{a,m,}$ which is the outcome we would have observed if exposure A had been set to value a and mediator M was set to m, and $M_{a,}$ value of mediator if exposure A was set to a. The nested counterfactual is $Y_{a*,\,M_a}$, the outcome we would have observed if A were set to a* and M to the value it would have taken if A were set to a. Model assumptions include (1) no unmeasured confounding of the exposure-outcome relationship, (2) no unmeasured confounding of the exposure-mediator relationship, (3) no unmeasured confounding of the mediator-outcome relationship, and (4) no unmeasured confounding of the mediator-outcome relationship after prior

exposure (Lange & Hansen, 2011; VanderWeele, 2011). Assumption 3 cannot be tested using observational data (Lange & Hansen, 2011).

To apply the counterfactual framework, we obtained unbiased estimates for direct and indirect effects from weighted Cox proportional hazards models with a duplicated dataset with two replications of the exposure. This approach is the same one used by Rochon, Bois, and Lange (2014). In the first replication, A^* is set to the original value of the exposure. In the second replication, A^* is set to the opposite (or "counterfactual") value of the exposure. Weights are determined by $W^c=P(M|A^*, C)/P(M|A, C)$, with proportions being derived from multivariable logistic regression model of persistent depressive symptoms, M, on baseline subclinical CVD (A and A^*) and baseline covariates, C (Rochon et al., 2014). Standard errors and 95% confidence intervals were determined by 5,000 bootstrap simulations (Lange & Hansen, 2011). The analysis with weighted Cox Proportional Hazards models was performed in R version 3.1.2 (*R: A Language and Environment for Statistical Computing*, 2013). All other analyses were done in Stata 13.0 (StataCorp, 2013).

Sensitivity Analysis

To examine whether confounding had an effect on both the exposure-mediator relationship and exposure-outcome relationship, we used propensity score matching, since the exposed and unexposed groups were unequally distributed (Ridgeway, McCaffrey, Morral, Burgette, & Griffin, 2014). Propensity scores were based on estimates from a multivariable logistic regression using baseline demographic

characteristics, (i.e., age, sex, race, poverty status, marital status, education level), ApoE ε4 status, and baseline depressive symptoms and assigned to participants. We performed diagnostic checks to assess the adequacy of matching (Ho, Imai, King, & Stuart, 2007; Ridgeway et al., 2014). We conducted the main statistical analysis with the matched data set. To account for small differences in the matched sample, we further adjusted the analysis by baseline covariates (Ho et al., 2007).

Results

Characteristics of the Study Sample

Table 1 shows baseline characteristics of the study sample stratified by presence (N=1,453) and absence (N=2,020) of baseline subclinical CVD. Those with subclinical CVD were more likely to be older, Caucasian, male, and impoverished, current smokers (all p's<0.01). Also, they had more depressive symptoms, lower HDL cholesterol, higher total cholesterol, higher systolic blood pressure, diabetes, and treated hypertension (all p's<0.01) (Table 1). As compared to those without baseline subclinical CVD, those with baseline subclinical CVD were less likely to be high school graduates and married, and they had less time on study (all p's<0.01). Those with and without baseline subclinical CVD were similar in terms of ethnicity, baseline depressive symptoms, ApoE ε4 status, antidepressant medications, and body mass index (all p's>0.05) (Table 1).

Table 2 shows the frequencies and percentages of the overall sample restricted to those without baseline clinical CVD. There were 456 (10.4%) who died within five years of baseline. About 17.6% (N=641) developed neither persistent depressive symptoms nor all-cause mortality, whereas 2.0% (N=74) developed only persistent depressive symptoms, 17.7% (N=352) died without persistent depressive symptoms, and 11.1% (N=406) died with persistent depressive symptoms (Table 2). Of those who died with persistent depressive symptoms, persistent depressive symptoms were present first prior to year 5 (100%) (Table 2).

Figure 2 shows Kaplan-Meier survival curves comparing the risk of all-cause mortality between those with and without baseline subclinical CVD. The cumulative proportion of all-cause mortality is higher among those with baseline subclinical CVD than those without baseline subclinical CVD ($p<0.01$). Participants contributed 55,157.06 person-years with a mean of 15.2 years (median of 15.9 years) between baseline and all-cause mortality, loss to follow-up, and end of follow-up in 2015.

Indirect Effect of Persistent Depressive Symptoms on the Association of Subclinical CVD with All-Cause Mortality

The total effect of subclinical CVD on all-cause mortality and its decomposition into natural indirect and direct effects is shown in Table 3. The total HR for the association between subclinical CVD and all-cause mortality was 1.58 (95% CI: 1.34, 1.87) (Table 3). The total HR was decomposed into a direct HR of subclinical CVD of 1.45 (95% CI: 1.34, 1.58) and indirect HR for persistent depressive symptoms of 1.09 (95% CI: 0.95, 1.25) (Table 3). Persistent depressive symptoms account for 18.8% for the total effect of subclinical CVD on all-cause mortality.

Sensitivity Analysis

To assess several assumptions of the counterfactual approach for causal mediation, we used propensity score matching. Figures 3 and 4 are the diagnostic plots for the propensity score matching. When we conducted the same analysis in a matched

sample and further adjusted the analysis by baseline covariates, we found that those with baseline subclinical CVD had 1.41 (95% CI: 1.30, 1.52) times the risk of all-cause mortality than those without baseline subclinical CVD (Table 4). When the total effect was decomposed into the direct and indirect effect, the direct effect (HR=1.41, 95% CI: 1.30, 1.52) explained 100% of the total effect between subclinical CVD and all-cause mortality. There was no indirect effect of persistent depressive symptoms (HR=1.00, 95% CI: 1.00, 1.00) (Table 4).

Discussion

Those with subclinical CVD were at an elevated risk of all-cause mortality, compared to those without subclinical CVD. Most of the total effect was explained by the direct effect of subclinical CVD on all-cause mortality. Persistent depressive symptoms explained 18.8% of the total effect of subclinical CVD on risk of all-cause mortality. When sensitivity analysis was conducted to further adjust for any potential confounding by propensity score matching, persistent depressive symptoms did not account for any of the total effect of subclinical CVD on all-cause mortality. These findings suggest that subclinical CVD is a risk factor of all-cause mortality and persistent depressive symptoms do not lie on that pathway.

The results are consistent with those from Almeida et al. (2012). They reported that depression and CVD were independently associated with all-cause mortality and that depression did not modify the association between CVD and all-cause mortality. Other studies have found that depression and subclinical CVD are independently associated with all-cause mortality, although these studies did not examine mediation of depression on the association between subclinical CVD and all-cause mortality (Ariyo et al., 2000; Kuller et al., 1995; Schulz et al., 2000).

One potential explanation for these results could be that the prevalence of depression remains stable until it declines during the 7th decade of life (Kessler et al., 2003) while the prevalence of clinical CVD, such as coronary heart disease, stroke, and atherosclerosis, increase exponentially with greater age (Bakhai, 2004). If vascular disease were related to late-onset depression, one would expect the prevalence of

depression to increase exponentially with greater age as well, but this trend is not observed (de Leeuw et al., 2001; Newson et al., 2010).

There are several strengths of this study. First, there is a large sample of older adults with repeated measures on depressive symptoms and all-cause mortality over a period of up to 24 years. Second, all-cause mortality is an outcome with over 98% ascertainment through the end of the study period we used, so we were able to measure the outcome without any missingness. Third, all causes of death were adjudicated by a committee of physicians. Fourth, investigators from the CHS developed an index of subclinical CVD based on objective measures (Kuller et al, 1995).

Despite the strengths of the study, there were several limitations. One limitation is the lack of clinical diagnosis of depression in CHS. However, the mCES-D may measure depressive symptoms in older adults who would not meet diagnostic criteria for depressive disorder. About 13% of the sample had persistent depressive symptoms 2-3 years after baseline, which is similar to the prevalence of depressive symptoms among community-dwelling older adults reported by Blazer (2003). Another limitation is the inability to test the assumption of unconfoundedness in observational studies, since the exposure was not randomized in the study sample. We limited the influence of confounding on the exposure-mediator and exposure-outcome relationships through propensity score matching, though. When we used the matched dataset, there was no evidence of an indirect effect of persistent depressive symptoms on the association between subclinical CVD and all-cause mortality.

To address concerns about confounding in the exposure-mediator and exposure-outcome associations, we adjusted the analysis by baseline covariates that were related to

exposure, mediator, and outcome. We introduced two-year lags to examine relative ordering of baseline subclinical CVD, persistent depressive symptoms measured 2-3 years after baseline, and all-cause mortality ascertained from at least five years after baseline. We conducted a sensitivity analysis with propensity scores based on baseline covariates to determine whether inferences remained.

Although baseline subclinical CVD had a positive effect on all-cause mortality, persistent depressive symptoms did not mediate the association between subclinical CVD and all-cause mortality. Persistent depressive symptoms and subclinical CVD both lead to all-cause mortality, but these conditions are independent of one another. The vascular pathway may be strongly correlated with all-cause mortality in older adults, such that depression does not have an effect on the association between subclinical CVD and all-cause-mortality.

There are a couple of future directions that may elucidate whether persistent depressive symptoms indirectly affect the association between subclinical CVD and all-cause mortality. The first would be to examine the indirect effect of each domain of the mCES-D on the association between subclinical CVD and all-cause mortality. A particular domain of the mCES-D may inform whether specific domains of depression, i.e., positive affect, depressed affect, somatic complaints, and interpersonal conflicts, may affect the association between subclinical CVD and all-cause mortality. Another direction would be to examine vascular processes in mid-life instead of late life. Late-onset depressive symptoms may mediate the association of mid-life vascular disease with all-cause mortality.

References

Alexopoulos, G.S., Meyers, B.S., Young, R.C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular Depression' Hypothesis. *Archives of General Psychiatry*, 54, 915-922.

Almeida, O.P., Alfonso, H., Flicker, L., Hankey, G.J., & Norman, P.E. (2012). Cardiovascular disease, depression and mortality: The Health in Men Study. *The American Journal of Geriatric Psychiatry*, 20(5), 433-440.

Andresen, E.M., Malmgren, J.A., Carter, W.B., & Patrick, D.L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventive Medicine*, 10(2), 77-84.

Ariyo, A.A., Haan, M., Tangen, C.M., Rutledge, J.C., Cushman, M., Dobs, A., . . ., Cardiovascular Health Study Collaborative Research Group. (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. *Circulation*, 102, 1773-1779.

Bakhai, A. (2004). The burden of coronary, cerebrovascular and peripheral arterial disease. *Pharmacoeconomics*, 22(4), 11-18.

Barefoot, J.C. & Schroll, M. (1996). Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*, 93(11), 1976-1980.

Bland, J.M., & Altman, D.G. (2004). The logrank test. *British Medical Journal*, 328(7447), 1073-1073.

Blazer, D. (2003). Depression in late life: Review and commentary. *Journal of*

Gerontology: Medical Sciences, 58A, 249-265.

Carnetheon, M.R., Biggs, M.L., Barzilay, J.I., Smith, N.L., Vaccarino, V., Bertoni, A.G., . . . Siscovick, D. (2007). Longitudinal association between depressive symptoms and incident Type 2 diabetes mellitus in older adults: The Cardiovascular Health Study. *Archives of Internal Medicine*, 167, 802-807.

Chaves, P.H.M., Kuller, L.H., O'Leary, D.H., Manolio, T.A., Newman, A.B., & Cardiovascular Health Study. (2004). Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *American Journal of Geriatric Cardiology*, 13(3), 137-151.

de Leeuw, F.E., de Groot, J.C., Achten, E., Oudkerk, M., Ramos, L.M.P., Heijboer, R., . . . Breteler, M.M.B. (2001). Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *Journal of Neurology, Neurosurgery & Psychiatry*, 70(1), 9-14.

Dickon, R.E. (2015). *Annual Update of the HHS Poverty Guidelines*. Washington, D.C.: Federal Register.

Fried, L.P., Kronmal, R.A., Newman, A.B., Bild, D.E., Mittelmark, M.B., Polak, J.F., . . . Cardiovascular Health Study Collaborative Research Group. (1998). Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA*, 279(8), 585-592.

Fried, L.P., Borhani, N.O., Enright, P., Furberg, C.D., Gardin, J.M., Kronmal, R.A., . . . Weiler, P.G. (1991). The Cardiovascular Health Study: design and rationale. *Annals of Epidemiology*, 1(3), 263-276.

Ho, D., Imai, K., King, G., & Stuart, E. (2007). Matching as nonparametric preprocessing

for reducing model dependence in parametric causal inference. *Political Analysis*, 15, 199-236.

Kaplan, E.L. & Meier, P. (1958). Non-parametric estimation from incomplete observations. *Journal of American Statistical Association*, 53, 457-481.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., . . . Wang, P.S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, 289(23), 3095-3105.

Kohout, Frank J., Berkman, Lisa F., Evans, Denis A., & Cornoni-Huntley, Joan. (1993). Two shorter forms of the CES-D depression symptoms index. *Journal of Aging and Health*, 5(2), 179-193.

Kuller, L.H., Arnold, A.M., Psaty, B.M., Robbins, J.A., O'Leary, D.H., Tracy, R.P., . . . Chaves, P.H.M. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the cardiovascular health study. *Archives of Internal Medicine*, 166(1), 71-78.

Kuller, L.H., Shemanski, L., Psaty, B.M., Borhani, N.O., Gardin, J., Haan, M.N., . . . Tracy, R. (1995). Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*, 92(4), 720-726.

Lange, T. & Hansen, J.V. (2011). Direct and indirect effects in a survival context. *Epidemiology*, 22(4), 575-581.

Newman, A.B., Sachs, M.C., Arnold, A.M., Fried, L.P., Kronmal, R., Cushman, M., . . . Lumley, T. (2009). Total and cause-specific mortality in the Cardiovascular Health Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 64A(12), 1251-1261.

Newson, R.S., Hek, K., Luijendijk, H.J., Hofman, A., Witteman, J.C.M., & Tiemeier, H. (2010). Atherosclerosis and incident depression in late life. *Archives of General Psychiatry*, 67(11), 1144-1150.

R: A Language and Environment for Statistical Computing. (2013). Vienna, Austria: R Foundation for Statistical Computing.

Ridgeway, G., McCaffrey, D., Morral, A., Burgette, L., & Griffin, B.A. (2014). *Toolkit for Weighting and Analysis of Nonequivalent Groups: A Tutorial for the R TWANG Package*. Santa Monica, CA: RAND Corporation.

Rochon, J., du Bois, A., & Lange, T. (2014). Mediation analysis of the relationship between institutional research activity and patient survival. *BMC Medical Research Methodology*, 14(1), 1-8.

Schulz, R., Beach, S.R., Ives, D.G., Martire, L.M., Ariyo, A.A., & Kop, W.J. (2000). Association between depression and mortality in older adults: The Cardiovascular Health Study. *Archives of Internal Medicine*, 160, 1761-1768.

Sheline, Y.I., Barch, D.M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., . . . Doraiswamy, P. M. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, 60, 58-65.

StataCorp. (2013). *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

VanderWeele, T. J. (2011). Causal mediation analysis with survival data. *Epidemiology*, 22(4), 582-585.

Table 1. Characteristics of participants from the Cardiovascular Health Study (N=3,473).

Baseline Characteristics	No Subclinical CVD N=1,453	Subclinical CVD N=2,020	p-value for difference
Age, mean(SD)	70.8 (4.4)	72.7 (5.2)	<0.01
White, n(%)	1,273 (87.6)	1,718 (85.1)	0.03
Hispanic, n(%)	18 (1.2)	21 (1.0)	0.86
Male, n(%)	467 (32.1)	805 (39.9)	<0.01
High School Graduate, n(%)	1,163 (80.0)	1,460 (72.3)	<0.01
Married, n(%)	1,018 (70.1)	1,337 (66.2)	0.02
mCES-D Score, mean (SD)	4.1 (4.1)	4.3 (4.2)	0.15
Poverty, n(%)	252 (17.3)	473 (23.4)	<0.01
ApoE ε4, n(%)	337 (23.2)	425 (21.0)	0.21
Diabetes, n(%)	78 (5.4)	188 (9.3)	<0.01
Current Smokers, n(%)	118 (8.1)	267 (13.2)	<0.01
Hypertension, n(%)	439 (30.2)	879 (43.5)	<0.01
Antihypertensive Medications n(%)	460 (31.7)	845 (41.8)	<0.01
Antidepressant Medications, n(%)	52 (3.6)	70 (3.5)	0.97
BMI, mean (SD)	26.4 (4.7)	26.7 (4.5)	0.06
SBP, mean (SD)	131.7 (19.1)	138.2 (22.0)	<0.01
Total cholesterol, mean (SD)	211.0 (36.1)	213.8 (39.9)	0.03
HDL cholesterol, mean (SD)	57.8 (16.1)	54.6 (15.5)	<0.01
Time on Study, mean (SD)	17.4 (5.4)	14.8 (5.6)	<0.01

SD=standard deviation, HDL=high density lipoprotein, mCES-D: modified Centers for Epidemiologic Studies: Depression Scale, SBP=systolic blood pressure, BMI=body mass index

Table 2. All-cause mortality and persistent depressive symptoms among participants without baseline clinical cardiovascular disease: Results from Cardiovascular Health Study (N=4,371)

	N (%)
Death within five years of baseline	456 (10.4%)
Developed neither persistent depressive symptoms nor all-cause mortality	641 (17.6%)
Developed only persistent depressive symptoms	74 (2.0%)
Developed only all-cause mortality	352 (17.7%)
Developed both	406 (11.1%)
Persistent depressive symptoms first before year 5	406 (100.0%)
All-cause mortality first before year 5	0 (0.0%)
Co-occurring with all-cause mortality	0 (0.0%)
Time in years from baseline to persistent depressive symptoms, mean (SD)	2.9 (0.1)
Time in years from baseline to all-cause mortality, mean (SD)	14.3 (6.6)

Note: For this table, we excluded those with baseline clinical cardiovascular disease (N=1,517).

Table 3. Causal mediation analysis using survival data: total, direct, and indirect effects from weighted continuous-time Cox Proportional Hazards Models of the association between subclinical cardiovascular disease and all-cause mortality via persistent depressive symptoms. Model was adjusted by race, sex, education level, marital status, age, ApoE ε4, depressive symptoms, and poverty status at baseline.

Effect (exposure vs. no exposure)	Hazard Ratio	95% Confidence Interval
Total Effect	**1.58**	**(1.34, 1.87)**
Direct Effect	**1.45**	**(1.34, 1.58)**
Indirect Effect (Through Mediator)	1.09	(0.95, 1.25)
Percent Mediated on Log HR Scale	18.84%	

HR=hazards ratios, CI=confidence intervals. Bolded values indicate that result was statistically significant at $p<0.05$.

NOTE: Percent mediated on the log HR scale was calculated as $[\ln(HR_{\text{indirect effect}})/\ln(HR_{\text{total effect}})]*100$.

Table 4. Sensitivity analysis with propensity scores - causal mediation analysis using survival data: total, direct, and indirect effects from weighted continuous-time Cox Proportional Hazards Models of the association between subclinical cardiovascular disease and all-cause mortality via persistent depressive symptoms. Model was adjusted by race, sex, education level, marital status, age, ApoE ε4 status, depressive symptoms, and poverty status at baseline.

Effect (exposure vs. no exposure)	Hazard Ratio	95% Confidence Interval
Total Effect	**1.41**	**(1.30, 1.52)**
Direct Effect	**1.41**	**(1.30, 1.52)**
Indirect Effect (Through Mediator)	1.00	(1.00, 1.00)
Percent Mediated	0.00%	

HR=hazards ratios, CI=confidence intervals. Bolded values indicate that result was statistically significant at $p<0.05$.

NOTE: Percent mediated on the log HR scale was calculated as $[\ln(HR_{\text{indirect effect}})/\ln(HR_{\text{total effect}})]*100$.

Figure 1. Hypothesized pathway linking subclinical cardiovascular disease, persistent depressive symptoms, and all-cause mortality. This figure illustrates persistent depressive symptoms partially mediating the association between subclinical cardiovascular disease and all-cause mortality.

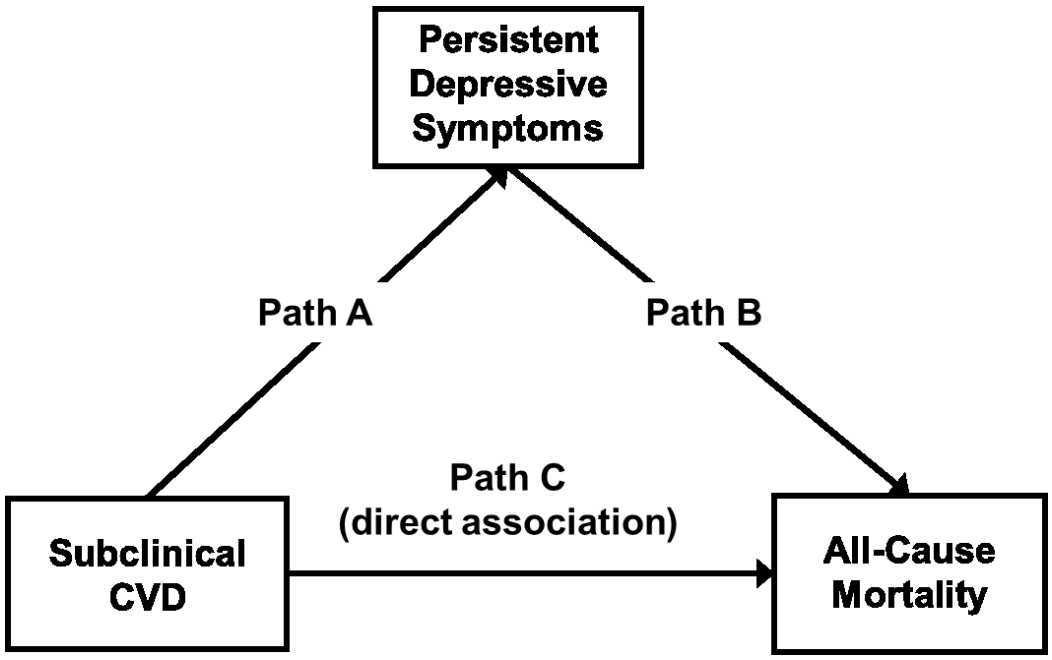


Figure 2. Kaplan-Meier plot of the association of baseline subclinical cardiovascular disease with all-cause mortality

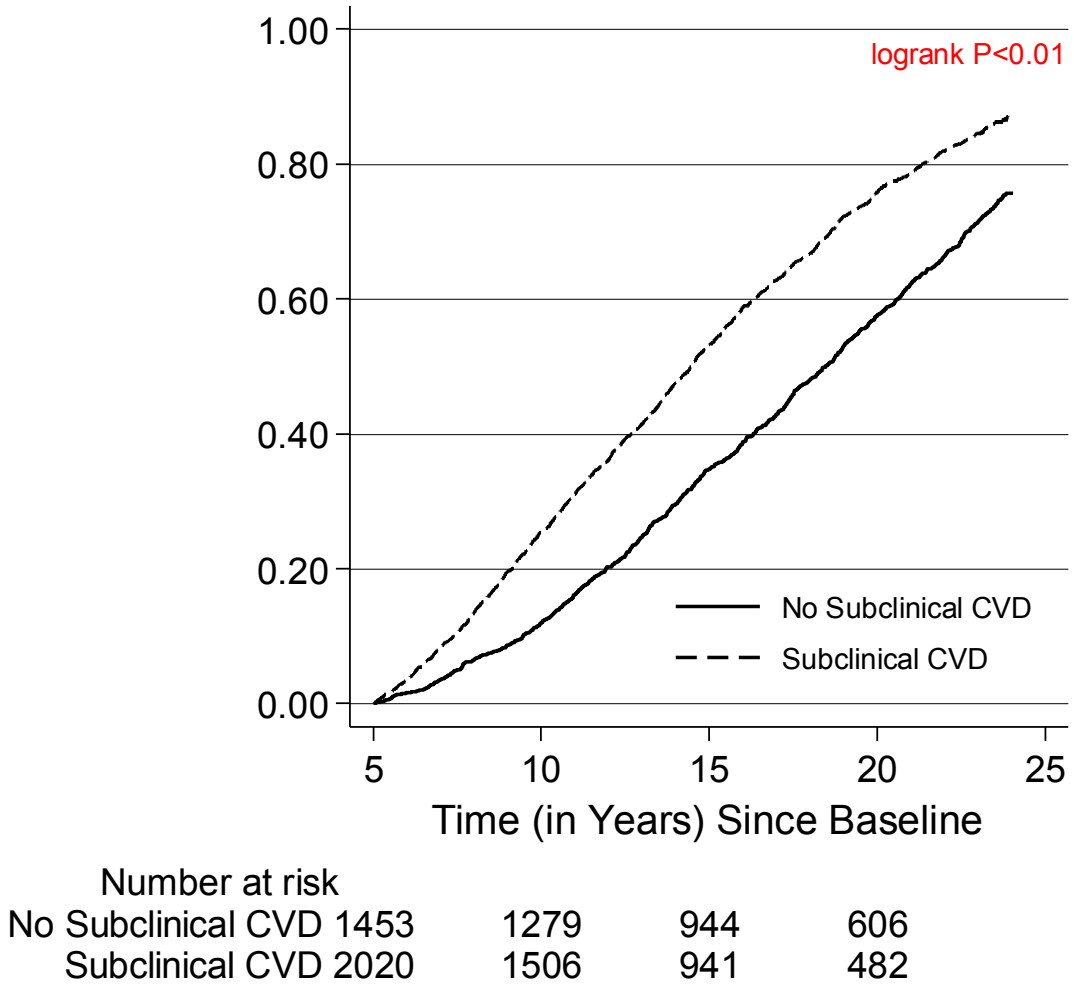
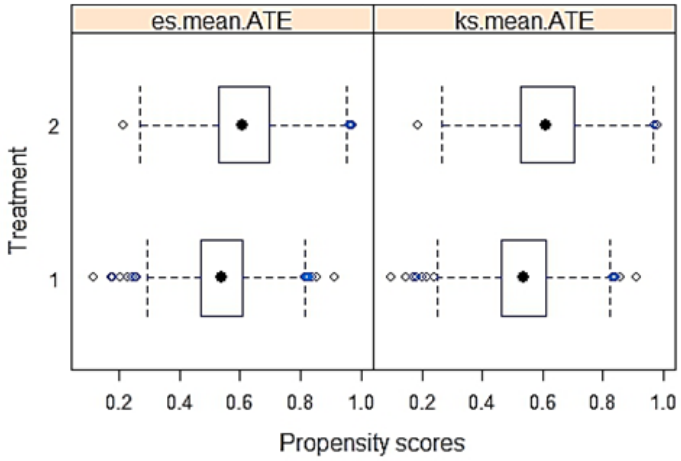
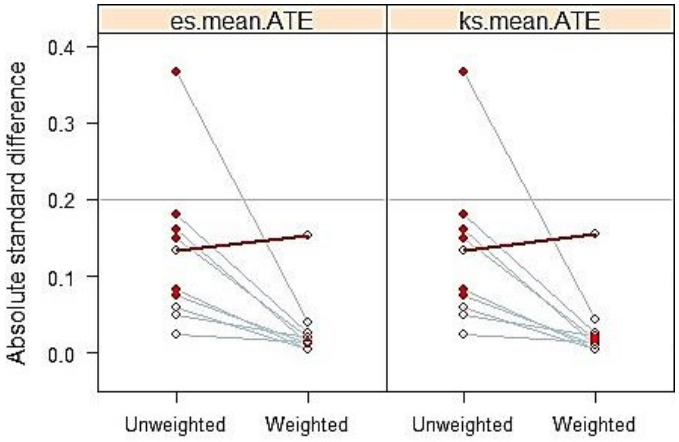


Figure 3. Diagnostic plots to compare two stopping rules (Effect Size [ES] and Kolmogorov-Smirnov [KS]) for propensity score matching by Average Treatment Effects (ATE)

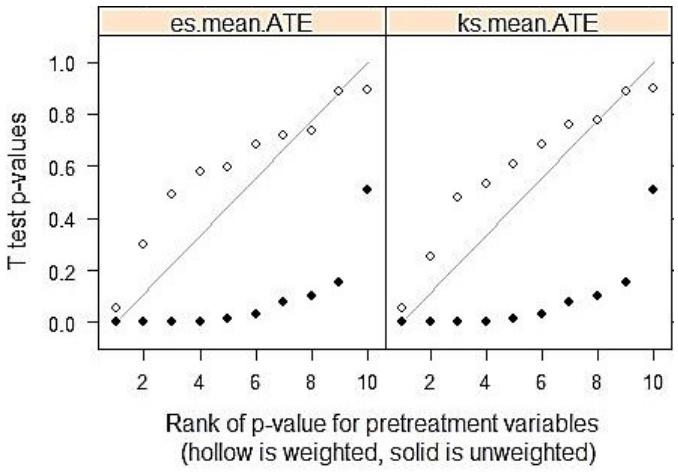
Panel A



Panel B



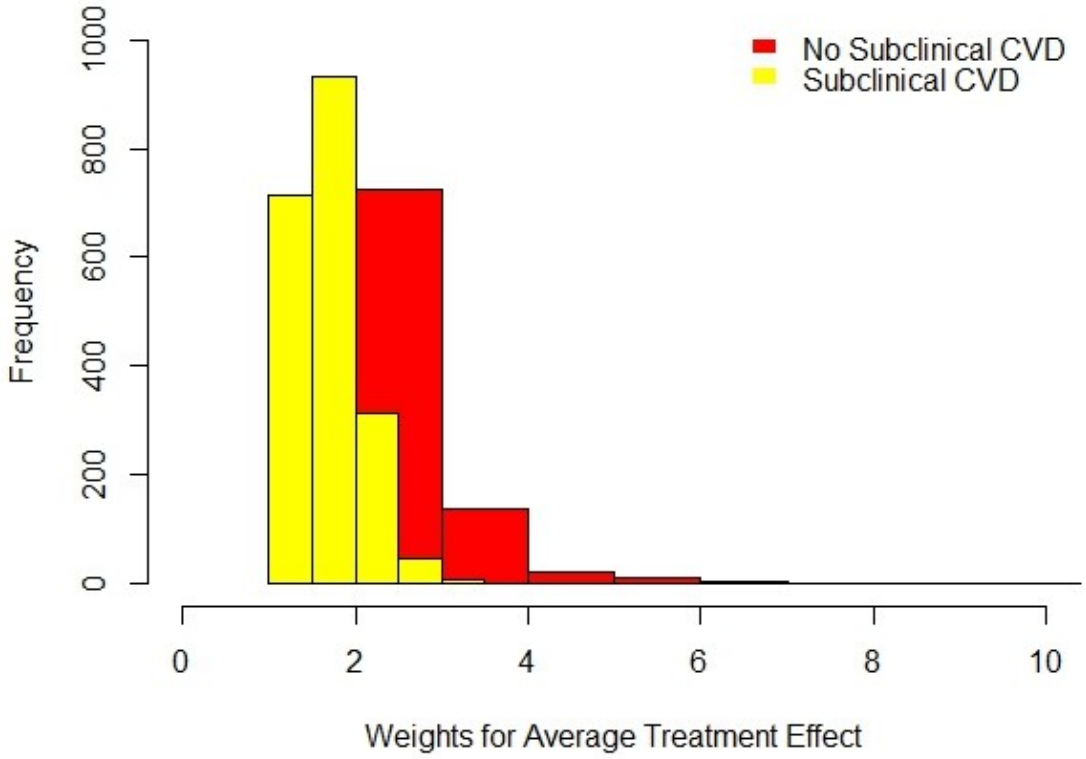
Panel C



Note: All Absolute standardized mean difference or Effect Size (es.mean.ATE) and Kolmogorov-Smirnov (ks.mean.ATE) test statistic. ES uses the effect size or the absolute standardized bias and summarizes across variables with the mean. KS uses KS statistics to assess balances and summarizes using the maximum across the variables.

Spread of the estimated propensity scores in the treatment and comparison groups for two stopping rules by boxplots (Panel A) and comparison between unweighted and weighted absolute standard differences (Panel B) and t-test p-values (Panel C).

Figure 4. Histograms for weights of propensity scores for the average treatment effect by baseline subclinical cardiovascular disease



Conclusions

Public health implications

Depression, although common in older adults, is undertreated. As the global population continues to age, treatment of depression will become a growing problem. Cardiovascular disease is already a common disease, and the top leading cause of death in the United States. Dementia is also one of the leading causes of death in the United States (James et al., 2014). These three diseases, depression, cardiovascular disease, and dementia, are associated with one another among older adults, but the way in which they are related is not clear. This study elucidated these relationships.

One plausible pathway in which cardiovascular disease, depression, and dementia are associated is proposed by the vascular depression hypothesis. Those with cardiovascular disease and dementia may have an underlying mood disorder, but the timing of these associations is unclear. Cardiovascular disease and depression could co-occur with one another, leading to an increased risk of developing dementia and subsequent death. Depression could lead to cardiovascular disease, or vice versa. In this study, we evaluated subclinical cardiovascular disease occurring prior to persistent depressive symptoms to determine whether persistent depressive symptoms partially mediated the association of subclinical cardiovascular disease with onset of mild cognitive impairment, dementia, and death.

This study provided insights regarding the role of depression in vascular pathways, changes in cognitive function, and mortality. Since depression is undertreated in older adults (Crystal, Sambamoorthi, Walkup, & Akincigil, 2003; García-Peña et al.,

2013; Newberg, Davydow, & Lee, 2006; Wittayanukorn, Qian, & Hansen, 2014), positive findings from this study would underscore the need for timely screening and treatment of depression among those with vascular risk factors to reduce risk of morbidity and decline in physical functioning as well as the burden on the utilization of health services (Crystal et al., 2003; Wittayanukorn et al., 2014).

Review of Specific Aim 1

In Specific Aim 1, we examined the effect of the timing of cardiovascular risk factors and vascular burden before and after age 65 on onset of incident depression among men, using data from the Johns Hopkins Precursors Study. We found that vascular burden after age 65, diabetes before and after age 65, hypertension before age 65, and hyperlipidemia before age 65 have strong associations with subsequent incident depression after age 65. We did not find associations between cardiovascular risk factors and onset of incident depression before age 65 with the exception of overweight/obese having a protective effect against incident depression before age 65. To account for the competing risk of death, we used Long-Gray method to examine subhazard ratios of associations of cardiovascular risk factors and onset of death before incident depression (Fine & Gray, 1999). Diabetes and ever smoking status were associated more with death than depression after age 65.

Review of Specific Aim 2

In Specific Aim 2, we evaluated the indirect effect of persistent depressive symptoms on the association of subclinical cardiovascular disease with onset of mild cognitive impairment and dementia, using data from the Cardiovascular Health Study. We found that persistent depressive symptoms partially mediated the association of subclinical cardiovascular disease with onset of mild cognitive impairment and dementia in older adults. This result still held when we matched the sample by propensity scores. Additionally, we evaluated the indirect effect of persistent depressive symptoms on the association between subclinical cardiovascular disease and dementia. There was no indirect effect of persistent depressive symptoms on the association between subclinical cardiovascular disease and incident dementia. However, those with baseline subclinical cardiovascular disease had an elevated risk of onset of incident dementia, compared to those without baseline subclinical cardiovascular disease.

Review of Specific Aim 3

In Specific Aim 3, we evaluated the mediating role of persistent depressive symptoms on the association between subclinical cardiovascular disease and all-cause mortality, using data from the Cardiovascular Health Study. We found that there was no indirect effect of persistent depressive symptoms on the association between subclinical cardiovascular disease and all-cause mortality in older adults. This finding suggests that subclinical cardiovascular disease and persistent depressive symptoms lie on independent pathways leading to all-cause mortality.

Study limitations

One important limitation is that the two cohort studies differed in terms of measurement of key constructs and timing thereof. The Johns Hopkins Precursors Study is a longitudinal observation study consisting of former medical students with approximately annual measures since early adulthood. Vascular burden was measured by a modified version of the Framingham Cardiovascular Disease Risk Score in the Johns Hopkins Precursors Study, and subclinical cardiovascular disease and mild cognitive impairment were not measured in the Johns Hopkins Precursors Study. The measures of depressive symptoms were limited to 2005 and 2007. First, we could not use consecutive scores from a two-year period, since depressive symptoms were collected in 2005 and 2007. If we used both scores from 2005 and 2007, then we would only be able to evaluate the outcome, starting in 2009. The end of the analytic period was 2011, thus allowing two years of assessment of the outcome.

While the Johns Hopkins Precursors Study has measures collected from early and middle adulthood, the Cardiovascular Health Study is limited to data collected on 5,888 men and women recruited from Medicare eligibility lists in later life. Midlife cardiovascular risk factors cannot be examined within this cohort. The Cardiovascular Health Study also lacks diagnosis of clinical depression, but has measures of depressive symptoms and neuropsychological tests approximately annually over an 18-year period.

Limitations specific to Specific Aim 1

Incidences of depression in our study are not comparable to nationally representative estimates because we excluded cases occurring before graduation, leading to lower incidence before age 65 than national estimates (Kessler & Wang, 2008). Additionally, physicians have higher rates of depression than the general population, thus the overall incidence rate in our sample of 22.3% is slightly higher than national estimates of 16.6% (Kessler & Wang, 2008).

Another caveat is other variables not incorporated into the analyses, i.e., genes and anxiety, could bias associations. Selection factors could also affect our study's generalizability; particularly, high socioeconomic status could have a protective effect against depression, thus leading to a potentially conservative estimate of risk related to depression (Ford et al., 1998). This limitation is also an advantage because the sample's homogeneity and selectivity ensures fewer unknown confounders. A third limitation is the small sample size and limited number of cases especially in the under-65 analysis, resulting in wide confidence intervals. Fourth, some participants (11%) died before age 65, thus death is a potentially competing outcome with depression after age 65 although sensitivity analyses showed no cardiovascular risk factors are associated with death prior to depression before age 65.

Limitations specific to Specific Aim 2

First, a main assumption of the mediation analysis is that all relevant confounders are included in the analysis. We included baseline demographic characteristics, baseline depressive symptoms, and ApoE ε4 as potential confounders in this analysis for

predictor, mediator, and outcome. Also, we conducted sensitivity analyses to determine if we still saw a similar result from the main analysis when the outcome was incident dementia. We also conducted the same analysis in a matched dataset based on propensity scores, and there was no change in inferences from the main analysis. Another limitation is the requirement of no other variables that confound the mediator-outcome association, but this is untestable in observational studies (Lange & Hansen, 2011). The third limitation is that an external replication analysis could not be performed, since there were very few cases of dementia in the Johns Hopkins Precursors Study.

Limitations specific to Specific Aim 3

One limitation is not having data on subclinical cardiovascular disease in mid-life. About one-fifth of the overall sample had prevalent cardiovascular disease at baseline, so they were excluded from the sample. If we could have ascertained subclinical cardiovascular disease prior to the development of cardiovascular disease, we may have had increased power to detect the indirect effect of persistent depressive symptoms on the association between subclinical cardiovascular disease and all-cause mortality. However, we found that those with baseline subclinical cardiovascular disease had an increased risk of all-cause mortality than those without baseline subclinical cardiovascular disease. The second limitation was the inability to replicate the analysis using an external cohort, the Johns Hopkins Precursors Study. There were 33 deaths with only three with depressive symptoms in 2005. Other limitations were the measurement of all relevant confounders in the causal mediation and no confounders in the mediator-outcome relationship. We

included baseline demographic characteristics, baseline depressive symptoms, and ApoE ε4, since these were associated with subclinical cardiovascular disease, persistent depressive symptoms, and all-cause mortality. As for confounders in the mediator-outcome relationship, this is not testable and can only be assumed.

Strengths

This current research has many strengths. Both cohort studies allowed for the evaluation of cardiovascular conditions, depressive symptoms, and outcomes, such as mild cognitive impairment, dementia and all-cause mortality, with at least 18 years of follow-up. The CHS has a large heterogeneous sample with measures on cardiovascular risk factors, neuropsychological tests, depressive symptoms, dementia, and mortality. The Johns Hopkins Precursors Study has repeated measures with up to 53 years of follow-up on former medical students for Aim 1. Measures have been validated in the sample, and diagnoses have been adjudicated by an independent committee of clinicians.

Strengths of the Johns Hopkins Precursors Study include available data over a long follow-up period and high response rates over the study, data on the diagnosis of clinical depression, and valid self-report measures on cardiovascular risk factors. In addition to the Johns Hopkins Precursors Study, the strengths of the CHS include a geographically diverse sample of community-dwelling older adults aged 65+ years in the United States with a long follow-up period (up to 18 years) and approximately annual assessments of depressive symptoms and biomarkers of cardiovascular function (Chaves et al., 2004; Kuller et al., 2006). Moreover, both the Johns Precursors Study and the CHS

have a high percentage of ascertainment on all-cause mortality, and both studies have expert committees that use standardized criteria for evaluating the onset of outcomes involving cardiovascular events.

References

Chaves, P.H.M., Kuller, L.H., O'Leary, D.H., Manolio, T.A., Newman, A.B., & Cardiovascular Health Study. (2004). Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *American Journal of Geriatric Cardiology*, 13(3), 137-151.

Crystal, S., Sambamoorthi, U., Walkup, J.T., & Akincigil, A. (2003). Diagnosis and treatment of depression in the elderly medicare population: Predictors, disparities and trends. *Journal of American Geriatric Society*, 51, 1718-1728.

Fine, J.P., & Gray, R.J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of American Statistical Association*, 94, 496-509.

Ford, D.E., Mead, L.A., Chang, P.P., Cooper-Patrick, L., Wang, N-Y, & Klag, M.J. (1998). Depression is a risk factor for coronary artery disease in men: The Precursors Study. *Archives of Internal Medicine*, 158(13), 1422-1426.

García-Peña, C., Wagner, F.A., Sanchez-García, S., Espinel-Bermudez, C., Juarez-Cedillo, T., Perez-Zepeda, M., . . . Gallo, J.J. (2013). Late-life depressive symptoms: Prediction models of change. *Journal of Affective Disorders*, 150, 886-894.

James, B.D., Leurgans, S.E., Hebert, L.E., Scherr, P.A., Yaffe, K., & Bennett, D.A. (2014). Contribution of Alzheimer disease to mortality in the United States. *Neurology*, 82(12), 1045-1050.

Kessler, R.C. & Wang, P.S. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annual Review of Public Health*, 29, 115-129.

Kuller, L.H., Arnold, A.M., Psaty, B.M., Robbins, J.A., O'Leary, DH, Tracy, RP, . . . Chaves, P.H.M. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Archives of Internal Medicine*, 166(1), 71-78.

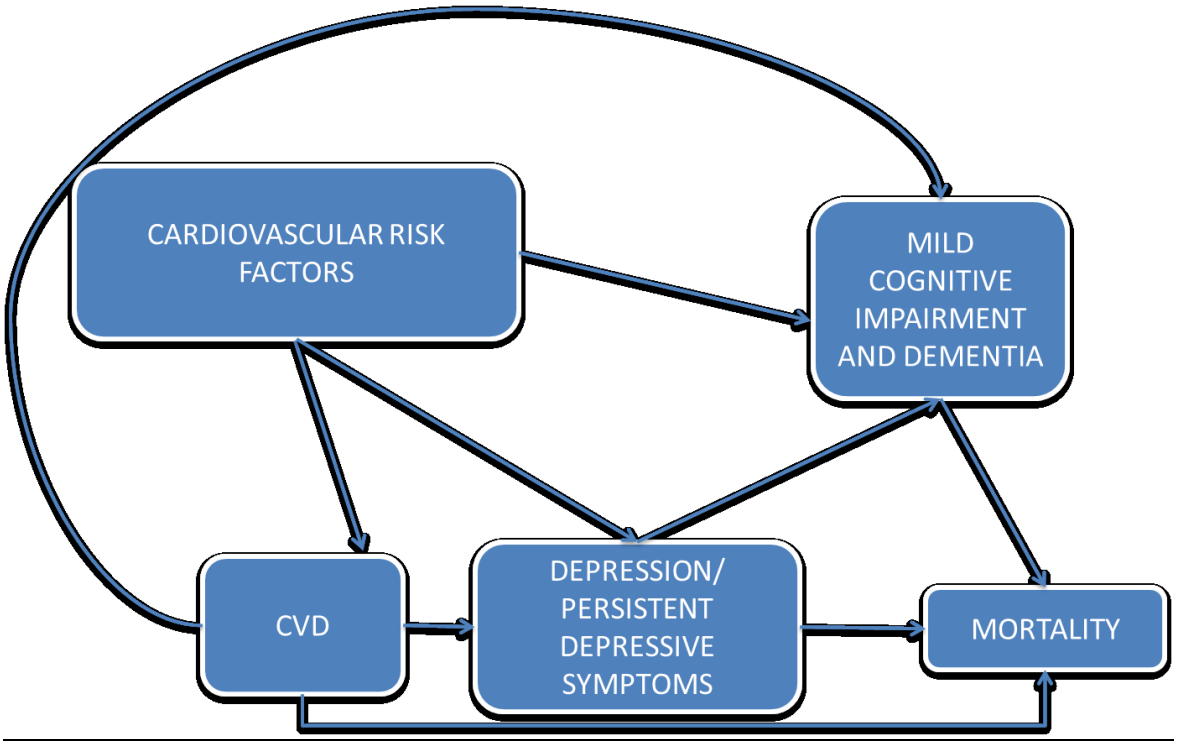
Lange, T. & Hansen, J.V. (2011). Direct and indirect effects in a survival context. *Epidemiology*, 22(4), 575-581.

Newberg, A.R., Davydow, D.S., & Lee, H.B. (2006). Cerebrovascular disease basis of depression: post-stroke depression and vascular depression. *International Review of Psychiatry*, 18(5), 433-441.

Wittayanukorn, S., Qian, J., & Hansen, R.A. (2014). Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. *General Hospital Psychiatry*, 36, 330-336.

Appendix 1: Conceptual Framework

Figure 1. Conceptual Framework for Study



Our specific aims are focused on the longitudinal analysis of cardiovascular risk factors, subclinical cardiovascular disease, depression/depressive symptoms, mild cognitive impairment, dementia, and mortality to determine whether the vascular depression hypothesis can be extended to include dementia and mortality. Figure 1 addresses the conceptual framework on the proposed project. First, we assess the temporal associations between vascular risk factors and late-life depression (Aim 1). Second, we will examine the indirect effect of persistent depressive symptoms on the association of subclinical cardiovascular disease with onset of mild cognitive impairment and dementia (Aim 2). Then, we will assess the indirect effect of persistent depressive symptoms on the association between subclinical cardiovascular disease and all-cause mortality (Aim 3).

CURRICULUM VITAE

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PERSONAL DATA

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EDUCATION AND TRAINING

Ph.D. 2017	*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health*
M.P.H. 2013	*Department of Epidemiology, The Joseph L. Mailman School of Public Health of Columbia University*
B.S. 2005	*Psychology, University of Maryland, College Park*
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PROFESSIONAL EXPERIENCE

Teaching Assistant, 2016-Present, Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

Research Assistant, 2014-Present, Departments of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health

Teaching Assistant, 2014-Present, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Clinical Research Coordinator, 2010-2013, The Eleanor and Lou Gehrig MDA/ALS Research Center, Columbia University Medical Center

Assistant Research Coordinator, 2008-2010, The Litwin-Zucker Center for Alzheimer's Disease and Memory Disorders, North Shore-Long Island Jewish Health System

Post-Baccalaureate Intramural Research Training Award Recipient, 2007-2008, Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke

Peace Corps Volunteer, 2005-2007, Program of Municipal Development, San Pedro de Copán, Honduras

PROFESSIONAL ACTIVITIES

Memberships

International Society to Advance Alzheimer's Research and Treatment (ISTAART), *2015-Present*

Gerontological Society of America (GSA), *2014-Present*

Gerontology Interest Group, Johns Hopkins Bloomberg School of Public Health, *2013-Present*

Association of Clinical Research Professionals (ACRP), *2012-2013*

Gerontological Society of America (GSA)

Abstract reviewer, 2015-Present

Gerontology Interest Group

Co-organizer, Annual Elizabeth L. Rogers Research on Aging Showcase, 2016

EDITORIAL ACTIVITIES

Ad hoc Reviewer

International Journal of Geriatric Psychiatry; Journal of the American Geriatric Society, Journal of Alzheimer's Disease; International Psychogeriatrics; Aging, Neuropsychology and Cognition; PLoS One; Journal of Aging and Physical Activity; American Journal of Geriatric Psychiatry

HONORS AND AWARDS

Pre-doctoral position on Training Grant (T32AG000247) on the Epidemiology and Aging Training Program, *Johns Hopkins Center on Aging and Health* (2013-Present)

Delta Omega Scholarship for Applied Research, *Johns Hopkins Bloomberg School of Public Health* (2016)

Student Travel Support Fund, *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health* (2016)

Complimentary Registration, *2016 Alzheimer's Association International Conference* (2016)

Department of Mental Health Centennial Essay Contest Award, *Department of Mental Health, Johns Hopkins Bloomberg School of Public Health* (2015)

Complimentary Registration, *6th International Workshop on HIV & Aging* (2015)

Public Health & Alzheimer's Disease Graduate Scholarship, *Alzheimer's Association and*
Centers for Disease Control and Prevention (2015)
Travel Award, *Gerontological Society of America* (2014)
1st Place in Student Category, *7th Annual Elizabeth L. Rogers Research on Aging Showcase,*
Johns Hopkins Bloomberg School of Public Health (2014)

Undergraduate
Certificate of Volunteerism, *Office of Maryland Governor Robert Ehrlich* (2004).
University Honors Program, *University of Maryland, College Park* (2001-2005)

PUBLICATIONS

Journal Articles (Peer-reviewed)

1. Armstrong, N.M., Meoni, L.A., Carlson, M.C., Xue, Q., Bandeen-Roche, K., Gallo, J.J., & Gross, A.L. (2017). Cardiovascular Risk Factors and Risk of Incident Depression throughout Adulthood: The Johns Hopkins Precursors Study. *Journal of Affective Disorders*, 214, 60-66.
2. Weiduschat, N., Mao, X., Hupf, J., Armstrong, N.M., Lange, D., Mitsumoto, H., & Shungu, D.C. (2014). Motor cortex glutathione deficit in ALS measured in vivo with the J-editing technique. *Neuroscience Letters,* 570C, 102-107.
3. Armstrong, N.M., Schupf, N., Grafman, J., & Huey, E.D. (2013). Caregiver burden in frontotemporal degeneration and corticobasal syndrome. *Dementia and Geriatric Cognitive Disorders*, 36(5-6), 310-318.
4. Huey, E.D., Koppel, J., Armstrong, N.M., Grafman, J., & Floeter, M.K. (2010). The prevalence of psychiatric disorders in PLS and ALS. *Amyotropic Lateral Sclerosis,* 11(3), 293-7.
5. Huey, E.D., Armstrong, N.M., Momeni, P., & Grafman, J. (2008). Challenges and new opportunities in the investigation of new drug therapies to treat frontotemporal dementia. *Expert Opinion on Therapeutic Targets,* 12, 1367-76.

Journal Articles (Submitted)

1. Armstrong, N.M., Gitlin, L.N., Parisi, J.M., Carlson, M.C., Rebok, G.W., & Gross, A.L. (2016). E Pluribus Unum: Harmonization of Physical Functioning across Intervention Studies of Older Adults. *Submitted to PLoS One.*
2. Armstrong, N.M., Surkan, P.J., Treisman, G.J., Sacktor, N.C., Irwin, M.R., Teplin, L.A., Stall, R.C., Martin, E.M., Becker, J.T., Munro, C., Levine, A.J., Jacobson, L.P., & Abraham, A.G. (2016). Association of Long-Term Patterns of Depressive Symptoms and Attention/Executive Function among Older Men with and without Human Immunodeficiency Virus. *Submitted to Journal of NeuroVirology.*

3. Armstrong, N.M., Surkan, P.J., Treisman, G.J., Sacktor, N.C., Irwin, M.R., Teplin, L.A., Stall, R.C., Jacobson, L.P., & Abraham, A.G. (2016). A comparison between a clinically-identified depressive phenotype and data-driven approaches in HIV-infected and HIV-uninfected men. Submitted to *Psychological Assessment*.

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PART II

TEACHING

Courses

Johns Hopkins Bloomberg School of Public Health
Teaching Assistant, *140.613.11, 140.614.11, 140.613.13, 140.614.13 Data Analysis Workshop I&II*, 2016-2017
Teaching Assistant, *140.656.01 Multilevel Statistical Models in Public Health*, 2016
Teaching Assistant, *140.655.01 Analysis of Longitudinal Data*, 2016
Teaching Assistant, *340.616.81 Epidemiology of Aging*, 2016
Teaching Assistant, *340.616.01 Epidemiology of Aging*, 2015-2016
Teaching Assistant, *340.608.60 Observational Epidemiology*, 2014
Teaching Assistant, *340.601.60 Principles of Epidemiology*, 2014
Teaching Assistant, *340.708.11 Advanced Methods in Observational Studies: Design*, 2014-2015
Teaching Assistant, *340.709.11 Advanced Methods in Observational Studies: Inference*, 2014-2015
Teaching Assistant, *280.350 Fundamentals of Epidemiology*, 2014

The Joseph L. Mailman School of Public Health of Columbia University
Teaching Assistant, *Program Planning, Design and Evaluation*, 2012

University of Maryland, College Park
Teaching Assistant, *Introduction to Biostatistics*, 2004

Guest Lectures (all Graduate, except where noted)

Epidemiology of Aging (340.616.01). *Epidemiology of Depression in Older Adults*. Johns Hopkins Bloomberg School of Public Health, April 2016
Epidemiology of Aging (340.616.81). *Epidemiology of Depression in Older Adults*. Johns Hopkins Bloomberg School of Public Health, January 2016
Senior-Level High School Biology Class. *Introduction to Public Health*, Western High School, November 2015

PRESENTATIONS

1. Armstrong, N.M., Krueger, F., and Grafman, J. (August 2005). Economic decision-making in two-person reciprocal trust games. Poster presentation at the NIH Summer Research Program Poster Day, Bethesda, MD.
2. Armstrong, N.M.**,** McElhiney, M., Rabkin, J., and Mitsumoto, H. (April 2011). Evaluation of Clinically Meaningful Changes in Patients with Amyotrophic Lateral Sclerosis. Poster presentation at Columbia University Mailman School of Public Health, Department of Epidemiology, Practicum Poster Day, New York, NY.
3. Weiduschat, N., Mao, X., Hupf, J., Armstrong, N.M., Mitsumoto, H., and Shungu, D.C. (April 2013). ^{1}H MRS Reveals Decreased Motor Cortex Glutathione in Patients with ALS. Poster presentation at the Annual Meeting for the American Academy of Neurology Emerging Science Poster Session, San Diego, CA.
4. Armstrong N.M., Meoni, L.A., Gallo, J.J., and Gross, A.L. (May 2014). Vascular Risk Factors and Cardiovascular Outcomes Associated with Late-Onset Depression: The Johns Hopkins Precursors Study. Poster presentation at the 7th Annual Elizabeth L. Rogers Research in Aging Showcase, Baltimore, MD.
5. Armstrong N.M., Parisi J.M., Gitlin L.N., Carlson M.C., Rebok G.W., and Gross A.L. (2014-2015). Harmonization of a Common Summary Measure of Physical Functioning Across 8 Datasets. Poster presentation at the 67th Annual Gerontological Society of America Scientific Meeting, Washington, D.C. (November 2014), the 2015 Delta Omega Scientific Poster Competition, Baltimore, MD (February 2015), and the 8th Annual Elizabeth L. Rogers Research in Aging Showcase, Baltimore, MD (May 2015).
6. Armstrong, N.M., Meoni, L.A., Gallo, J.J., and Gross, A.L. (November 2014). Vascular Risk Factors Associated with Time to Incident Depression: The Johns Hopkins Precursors Study. Poster presentation at the 67th Annual Gerontological Society of America Scientific Meeting, Washington, D.C.
7. Armstrong, N.M., Surkan, P.J., Gross, A.L., Treisman, G.J., Sacktor, N.C., Irwin, M., Wolinsky, S. Stall, R., Jacobson, L.P., and Abraham, A.G. (October 2015). Longitudinal Association between Depressive Phenotype and Cognitive Impairment in Men with and without HIV. Symposium presentation at the 6th International Workshop on HIV & Aging, Washington, D.C.
8. Armstrong, N.M., Gross, A.L., Varma, V.R., Tian, J., and Carlson, M.C. (2015). Model-Estimated Intercept During the Color Condition of Stroop Test Predicts Onset of Dementia. Poster presentation at the Department of Epidemiology Centennial Poster Competition, Baltimore MD (October 2015) and 68th Annual Gerontological Society of America Scientific Meeting, Orlando, FL (November 2015).
9. Armstrong, N.M., Carlson, M.C., Xue, Q., Carnethon, M.R., Rosano, C., Chaves, P.H.M., Bandeen-Roche, K., and Gross, A.L. (April 2016). Mediation of the Association of Cardiovascular Risk Factors with Cognitive Change by Depressive Symptoms: Cardiovascular Health Study. Poster presentation at the 2016 Cognitive Aging Conference, Atlanta, GA.

10. Armstrong, N.M., Carlson, M.C., Xue, Q., Carnethon, M.R., Rosano, C., Chaves, P.H.M., Bandeen-Roche, K., and Gross, A.L. (July 2016). Depressive Symptoms as Potential Mediators of the Associations of Vascular Burden and Subclinical Cardiovascular Disease with Cognitive Decline: Cardiovascular Health Study. Poster presentation at the Alzheimer's Association International Conference (AAIC 2016), Toronto, Canada.
11. Armstrong, N.M., Surkan, P.J., Gross, A.L., Treisman, G.J., Sacktor, N.C., Irwin, M., Wolinsky, S. Stall, R., Jacobson, L.P., and Abraham, A.G. Differences in the Association between Depressive Phenotype and Cognitive Trajectories by HIV Status. Poster presentation at the 7th International Workshop on HIV & Aging, Washington, D.C. (October 2016) and the 2017 Delta Omega Scientific Poster Competition, Baltimore, MD (March 2017).
12. Armstrong, N.M., Gross, A.L., Andrews, R., Varma, V.R., Xue, Q., Carlson, M.C. (November 2016). Association between Trial-Level Change in Stroop Test and Mobility: Baltimore Experience Corps Trial. Poster presentation at the 69th Annual Gerontological Society of America Scientific Meeting, New Orleans, LA.